Neuroinflammation and excitatory symptoms in bipolar disorder

Isabella Panaccione1,2,3, Gianfranco Spalletta2,4, Gabriele Sani1,2,3

1Department of Neuroscience, Mental Health and Sensory Organs, School of Medicine and Psychology, Sapienza University of Rome, Sant’Andrea Hospital, 00189 Rome, Italy.
2Department of Clinical and Behavioural Neurology, Neuropsychiatry Laboratory, IRCCS Santa Lucia Foundation, 00179 Rome, Italy.
3Centro Lucio Bini, 00193 Rome, Italy.
4Menninger Department of Psychiatry and Behavioral Sciences, Beth K and Stuart C Yudofsky Division of Neuropsychiatry, Baylor College of Medicine, Houston, TX 77030, USA

ABSTRACT

Neuroinflammation has been proposed as a strong biological factor underlying the development of neuropsychiatric diseases. A role for dysregulation of the immune system was initially suggested in depressive disorders and subsequently extended to other illnesses, including bipolar disorder (BD). Indeed, there is growing evidence confirming the presence of a generalized pro-inflammatory state in BD patients, involving alterations in cytokine, acute-phase proteins, and complement factor secretion, white blood cell differentiation, microglial activation, arachidonic acid signaling pathways, and increased oxidative stress markers. Medications commonly used to treat BD, such as lithium, antiepileptics and antipsychotics, show some immunoregulatory activity both in vitro and in vivo. The aim of our study was to review the role of different inflammatory mechanisms, specifically in the development of excitatory symptoms, via a systematic PubMed search of the literature. Despite the high variability of results among studies, we found evidence indicating specific alterations of the inflammatory response during manic and mixed states of BD. These findings may help to clarify some of the complex mechanisms underlying the development of excitatory symptoms and suggest a potential role for drugs targeting the inflammatory system as new therapeutic options.

Key words: Anti-inflammatory drugs, bipolar disorder, glia, interleukin, mania, mixed states, neuroinflammation

INTRODUCTION

Amongst the wide constellation of factors thought to be involved in the pathophysiology of mental illness, there’s accumulating evidence for a pivotal role of the inflammatory system as a risk factor for neuropsychiatric disease onset and progression.1-3 In the early 1970s, several studies showed how the brain is able to modulate the immune system, focusing on the role of stress and associated hypothalamus-pituitary axis mechanisms. These observations have been translated in studies involving patients diagnosed with the major depressive disorder. Indeed, both the clinical observation of high rates of depressive symptoms in patients affected by immune-related diseases, such as cancer, diabetes, and cardiovascular, inflammatory, and autoimmune diseases, and the results of a majority of studies investigating the role of inflammation in depressive disorders confirmed this hypothesis.4,5 The link between depressive symptoms and systemic inflammation is strengthened by the experimental observation that the injection of interleukin (IL)-1β or tumor necrosis factor (TNF)-α in animals produces a range of behavioral abnormalities known as “sickness behavior”. Mice show reductions in locomotor activity, social interaction, novelty seeking behavior, saccharine preference, brain self-stimulation, and food and water intake, as well as impairments in learning and memory.6-8

Corresponding Author: Dr. Gabriele Sani, Department of Neuroscience, Mental Health and Sensory Organs, School of Medicine and Psychology, Sapienza University of Rome, Sant’Andrea Hospital, Via di Grottarossa, 1035/39, 00189 Rome, Italy. E-mail: gabriele.sani@uniroma1.it

Access this article online

Quick Response Code:

Website: www.nnjournal.net

DOI: 10.4103/2347-8659.167304


Received: 06-04-2015; Accepted: 05-05-2015

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: nn_editor001@nnjournal.net

© 2015 Neuroimmunology and Neuroinflammation | Published by Hongkong Partner Publishing Co. Limited

215
In humans, treatment with interferon (IFN)-α induces depressive symptoms such as anhedonia, fatigue, suicidal thoughts, cognitive impairments, loss of appetite, and sleep alterations.\[^{[8,10]}\] (therefore hinting that IFN-α may contribute to the development of mood disorders.\[^{[11,12]}\] Healthy volunteers injected with *Salmonella abortus equi* endotoxin show increased circulating levels of inflammatory mediators and develop psychiatric symptoms, such as anxiety and depressed mood, as well as mild, transient cognitive impairments.\[^{[13]}\] Depressed patients with no other concomitant medical conditions show alterations in the levels of many pro-inflammatory cytokines and acute-phase proteins, both in peripheral blood and cerebrospinal fluid (CSF).\[^{[14]}\] In particular, variations in the concentration of IL-1, IL-6, TNF-α, and C-reactive protein (CRP) have been observed in patients diagnosed with depressive disorders when compared to healthy controls.\[^{[15‑26]}\] Glial abnormalities,\[^{[21‑23]}\] increased oxidative stress,\[^{[24‑27]}\] macrophage activation,\[^{[28‑30]}\] and alterations in the arachidonic acid (AA) signaling cascade\[^{[31‑35]}\] have also been described in depressed patients. Taken together, these results confirm the substantial involvement of the immune system in the mechanisms of depressive disorders, possibly via interactions between the immune system and the neuroendocrine and autonomic nervous system.\[^{[36‑40]}\]

Starting from these observations, the role of the immune system has been investigated in other neuropsychiatric diseases, including bipolar disorder (BD), schizophrenia, anxiety disorders, and personality disorders. A chronic inflammatory state that exacerbates during symptomatic relapses has been suggested to be involved in the pathophysiology of BD.\[^{[41]}\] Interestingly, therapy with IFN-α has been reported several times to induce manic/hypomanic or mixed states in nonpsychiatric patients.\[^{[42‑45]}\] One study highlighted the higher prevalence of mild excitatory symptoms (i.e. irritable mood, racing thoughts, distractibility, agitation, and insomnia) associated with anhedonia and fatigue in IFN-α treated patients, rather than typical major depressive or euphoric symptoms.\[^{[46]}\] Another study found that nonpsychiatric patients are more likely to develop depressive symptoms following a therapy with IFN-α if they experienced lifetime subthreshold manic/hypomanic symptoms.\[^{[47]}\] Similarly to what has been observed in depression, there is a high rate of comorbidity between BD and other inflammation-related medical conditions, such as diabetes, metabolic syndrome, and cardiovascular and cerebrovascular diseases,\[^{[46‑50]}\] which led some authors to question if BD could be considered as a multi-system inflammatory illness.\[^{[41]}\]

Many studies conducted on BD patients have demonstrated increased levels of pro-inflammatory markers, both in the blood and in the brain, that is, abnormal T-cell and monocyte-macrophage activation, alterations in chemokine, cytokine, prostaglandin, and acute-phase protein synthesis, aberrant inflammatory-related gene expression, increased oxidative stress markers, and microglial activation.\[^{[28‑32,34‑47]}\] The vast majority of studies focused on assessing peripheral cytokine levels. Despite some mixed results, globally BD patients show higher serum concentrations of TNF-α, soluble TNF-receptor 1 (sTNF-R1), IL-1β, IL-4, soluble IL-2 receptor (sIL-2R), and sIL-6 receptor (sIL-6R) compared to healthy controls, as well as a nearly-significant trend for IL-6.\[^{[54‑60,70]}\] These results refer to both euthymic and symptomatic BD patients and do not emphasize the possible differences in the cytokine expression patterns correlated with the presence of excitatory symptoms. We, therefore, performed an analysis of the literature aimed at highlighting the possible presence of alterations in immune system activity, specifically in relation to excitatory symptoms of BD. We also briefly examined the possible use of anti-inflammatory drugs as add-on therapies to improve clinical outcomes.

We performed a literature review through a careful search of articles using PubMed. We conducted an initial search using keywords such as “affective disorder” or “major depression” or “bipolar dis*” and “inflamm*” to provide context. Subsequent searches were performed using the following key words: “bipolar dis*” and/or “mania” or “manic” or “mixed” or “depressi*”, cross-referenced with a set of inflammation-related terms, such as “cytokine”, “IL”, “glia”, “oxidative stress”, and “AA”. To examine the role on the immune system of drugs commonly used to treat excitatory symptoms, we cross-referenced the above-mentioned set of inflammatory-related keywords with “lithium”, “mood-stabilizing agents”, and “antipsychotics”. Finally, to identify studies on the possible role of anti-inflammatory drugs in the management of affective episodes, we cross-referenced the mood-related keywords mentioned earlier with the terms “anti-inflammatory drugs”, “coxib” and “anti-TNF-α”.

Reference lists from selected papers were subsequently searched to identify further relevant literature. We limited the search to papers written in English. There were no timeframe limitations in our searches. Data on alterations of the inflammatory system in excitatory phases of BD (mania, hypomania and mixed states) are presented together because most of the studies do not specifically differentiate between the three.
IMMUNE SYSTEM ALTERATIONS AND EXCITATORY SYMPTOMS IN AFFECTIVE DISORDERS

Inflammation in manic, hypomanic and mixed states

Cytokines are low-molecular-weight proteins secreted by immune cells, such as white blood cells and microglia, which play a crucial role in modulating the inflammatory response. In the brain, cytokines exert immune protection by promoting the elimination of damaged neurons and have also been demonstrated to influence neurogenesis and cell survival.[71] However, dysregulation of cytokine synthesis and activity is known to lead to alterations of synaptic transmission and synaptic plasticity, neurotoxicity, and neuronal death.[88]

An imbalance between pro- and anti-inflammatory cytokines has been suggested to exist in manic patients versus healthy controls,[72] underlying a more pronounced shift toward a pro-inflammatory status in acute relapses. There is also evidence of an imbalance between cytokines secreted by type 1 T helper (Th1) lymphocytes and type 2 T helper (Th2) lymphocytes during mania, with an increased Th1/Th2 ratio that normalizes after treatment.[73] IL-1β levels are increased in the CSF of euthymic bipolar patients with at least one manic/hypomanic episode in the last year when compared with patients without a recent episode.[74] Peripheral IL-1β concentrations also positively correlate with suicide risk in BD patients,[75] and suicide risk is now known to be much higher when excitatory symptoms are present during relapses.[76,77] IL-1 receptor antagonist (IL-1Ra) serum concentrations are higher in bipolar patients both in mania and partial remission, whereas they normalize when full remission is achieved.[78] Several studies investigating serum concentrations of IL-8, as well as IL-2, IL-6 and their soluble receptors: IL-2 receptor (sIL-2R) and IL-6 receptor (sIL-6R), found that levels are higher in manic patients than in healthy controls.[79-81] In particular, peripheral concentrations of IL-2, IL-6, and their receptors have been found to positively correlate with the severity of symptoms and tend to normalize following treatment and during remission.[78,72,79,80,82] A recent study by Tsai's group[83] also showed that concentrations of serum IL-6R reflected illness activity in a BD patient with manic relapses during a 63-week observation time. These findings, though, were only partially confirmed by meta-analyses that demonstrated increased peripheral expression of sIL-2R in manic patients, with just a trend toward the higher expression of IL-6 and sIL-6R.[69,70,84] Levels of both TNF-α and its receptor, tumor necrosis factor receptor type 1 (sTNF-R1), are increased in manic BD patients compared to healthy controls and euthymic patients.[84] Elevated TNF-α levels observed in mania do not normalize after treatment, suggesting that TNF-α may be considered as a trait marker of disease.[72] This hypothesis is supported by the finding that serum TNF-α concentrations in BD patients are higher than in controls both in early (< 3 years) and late stages (> 10 years) of the disease, and that TNF-α levels are higher in late-stage than in early-stage patients.[85] However, a study from Guloksuz et al.[86] demonstrated by flow cytometry that measured levels of TNF-α are higher in lithium-treated, but not medication-free euthymic BD patients compared to healthy controls, suggesting that the persistently increased levels of TNF-α might result as an effect of lithium therapy rather than reflect a persistent pro-inflammatory inter-episodic status. It is interesting to note that TNF-α has been demonstrated to modulate inflammation and neurotransmission in brain regions regulating impulse control, like the prefrontal cortex and anterior cingulate cortex (ACC).[87] The expression of some TNF-related genes correlates with ACC activation and aggression in BD children and adolescents.[88] Moreover, serum TNF-α concentrations correlate with deficits in executive functioning, that is, inhibitory control, in BD patients,[89] inhibitory control is much more impaired in manic/mixed than in euthymic or depressed BD patients.[90] Levels of sTNF-R1 positively correlate with elevated mood, being increased in manic states compared to depression,[91,92] and are much higher in BD-I than in BD-II patients.[88] Plasma levels of sTNF-R1 also positively correlate with general disease gravity and psychotic features in BD patients.[93]

The alterations in the expression of TNF-α in BD are quite intriguing since this factor is involved in many processes, such as synaptic transmission, synaptic plasticity, neurodevelopment, neurotoxicity, and regulation of neuronal survival.[94,95] Increased expression of TNF-α during acute mood episodes is thought to shift the balance between cellular survival and cellular death toward apoptosis,[96] therefore playing a role in the neurodegeneration observed in chronic BD patients and possibly in cognitive impairment.[97] Furthermore, TNF-α induces central recruitment of circulating monocytes during peripheral inflammation by cerebral microglia,[98] which in turn produces more pro-inflammatory cytokines, sustaining the inflammatory status.[99]

C-reactive protein is a nonspecific acute-phase protein, synthesized by hepatocytes in response to IL-1 and IL-6 secretion during inflammatory processes. CRP levels in BD patients rise during both mania and depression and remain higher than in controls in partial and full remission of symptoms,[78,83,100] suggesting a constant, nonspecific activation of immunomodulatory processes. Nevertheless, other studies have found increased levels of CRP only in manic bipolar patients and not in depressed or euthymic patients,[101] and that...
the increase in CRP levels positively correlates with the severity of manic symptoms.\cite{102,103}

The complement system is a part of the innate immune system. It consists of over 30 different proteins and its activation ultimately leads to a massive amplification of the immune response. Increased levels of complement factors C3, C4, and C6 have been found in BD patients during mania.\cite{104}

Several studies have demonstrated an abnormal activation of T-cells in bipolar patients, regardless of the phase\cite{38} whereas others have found an increase in T-cell proliferation and activation during manic states that normalized after full remission.\cite{105,106} A recent study demonstrated an increased proportion of circulating monocytes in BD patients,\cite{107} and a correlation between a subcluster of monocyte proinflammatory gene (i.e. CCL2 and CCL7) expression and excitatory symptoms was found.\cite{108} Interestingly, total leukocyte counts are higher in mixed states than in pure manic states, and this difference appears to be due mainly to an increased number of neutrophils and monocytes.\cite{109}

Oxidative stress is defined as the imbalance between oxidant and anti-oxidant agents, provoking macromolecular and cellular damage and ultimately inducing impairments in neuronal survival, plasticity, and signal transmission.\cite{110} Alterations in the oxidative status have been found to differ within mood states in BD patients. Peripheral levels of nitric oxide (NO), a powerful oxidant agent, are higher in BD patients, especially during mania, and also positively correlate with the number of lifetime manic episodes.\cite{111,112} When compared with euthymic subjects or healthy controls, manic patients show higher levels of thiobarbituric acid reactive substances (TBARS) and protein carbonyl content (PCC), peripheral markers of lipid peroxidation and oxidative damage to proteins, respectively.\cite{113} TBARS levels normalize after treatment with mood stabilizers and anti-psychotic drugs.\cite{114} Levels of superoxide dismutase, a main component of the anti-oxidant defense system, are also higher in BD patients during mania, suggesting a compensatory response to increased oxidative stress.\cite{115} The imbalance in the oxidative state of manic BD patients is normalized by lithium treatment.\cite{116}

Arachidonic acid is one of the most abundant fatty acids in the brain and is a precursor in the production of prostaglandins (PG). PG are hormone-like lipid compounds, synthesized from AA by cyclooxygenase (COX) isoenzymes, and play crucial roles in the promotion of systemic inflammation.\cite{117} Protein and mRNA levels of COX isoform-2 (COX-2) and other AA signaling pathway enzymes, such as phospholipase A2 (PLA2) and membrane prostaglandin E synthase, are higher in the postmortem frontal cortex of bipolar patients than in healthy controls.\cite{118} A recent study suggests that some of these alterations might be due to epigenetic mechanisms.\cite{119} Among other pro-inflammatory stimuli, COX-2 expression is induced by TNF-α.\cite{120,121} The production of which has been found to be increased during manic relapses of BD as already described. Lamotrigine and valproic acid, two widely used mood stabilizing agents, decrease COX-2 expression in rat frontal cortex.\cite{122,123} Unlike lamotrigine,\cite{124} however, agents known to be effective in treating mania, such as lithium, carbamazepine, valproate, and the anti-psychotic drugs clozapine and olanzapine, also decrease AA turnover in rat brain.\cite{125,126} Eventually modulating dopaminergic and glutamatergic transmission.\cite{127,128} On the other hand, the antidepressants fluoxetine and imipramine, but not bupropion, increase AA signaling and turnover in the rat brain.\cite{129,130} These findings are intriguing, considering that antidepressant treatment in bipolar patients often leads to a switch from a depressive to a manic/hypomanic state\cite{131,132} and that, among antidepressants, bupropion is the drug associated with the lowest risk of inducing switching.\cite{133,134} Taken together, these findings suggest that manic/hypomanic phases might be associated with a higher rate of AA signaling, an interesting hypothesis that would need more in-depth research.\cite{135} Novel neuroimaging techniques such as positron emission tomography with 11C-labeled fatty acids might help to better clarify the AA turnover and signaling cascade in the brain of BD patients and its role in the development of symptoms.\cite{136}

Microglial cells are the resident macrophages of the central nervous system and play critical roles both in physiological and pathological functioning of the brain, as well as during neurodevelopment.\cite{137} One of the most important activities of microglial cells is to regulate inflammation within the CNS via the production of pro-inflammatory cytokines and free radicals, as well as anti-inflammatory components.\cite{138} Aberrant microglial cell number and function are involved in the pathophysiology of psychiatric disorders, including BD,\cite{139,140,141} possibly modulating GSK-3β/Wnt pathway activity through neuroinflammation.\cite{142} However, to date, little is known about direct correlations between excitatory symptoms and glial activity.\cite{143} During acute manic states, alterations in neuronal/glial interactions and glutamatergic transmission have been demonstrated by proton magnetic resonance spectroscopy.\cite{144} Some additional evidence on this issue has been provided by animal experiments.
Mice lacking the alpha-2 isoform of Na+/K+-ATPase, also known as the sodium pump, show some manic-like behavior (i.e., hyperlocomotion), and hyperlocomotion is prevented by pretreatment with lithium.\cite{155} Na+/K+-ATPase inhibitors, such as ouabain, have been extensively used in animal experiments to model BP.\cite{156} The alpha-2 isoform is expressed exclusively in glial cells\cite{157} and is reduced in postmortem temporal cortex of BD patients.\cite{158}

**Inflammation and excitatory symptoms in depression**

Markers of increased immune-inflammatory activity have been demonstrated in patients diagnosed with the major depressive disorder or unipolar depression (UD). These findings have been further confirmed by meta-analyses,\cite{159,160} but the studies included in the research, if considered individually, did not present homogeneous results. This might be explained by methodological differences in conducting the studies and/or by a variety of confounding factors, one of which might be the presence of some subthreshold excitatory symptoms in depressed patients such as mood lability, inner tension, irritability, racing and crowded thoughts, talkativeness, sleep disturbances, and psychomotor agitation.\cite{161–163} These symptoms are often misidentified in clinical practice,\cite{164–166} despite being present in around 40% of patients diagnosed with depression.\cite{167,168} In addition, about 20% of subjects initially diagnosed with the major depressive disorder and without lifetime manic symptoms develop excitatory features during the course of their disease.\cite{169}

A recent study found significantly elevated baseline levels of CRP in patients diagnosed with UD that later developed excitatory symptoms compared to unipolar depressed patients who did not show manic symptoms over two years follow-up.\cite{170} A similar, but nonsignificant, trend toward higher levels of IL-6 and TNF-α was also observed.\cite{171} Both the presence of excitatory symptoms during the depression and high levels of serum cytokines before treatment are associated with a more severe course of the disease and poor response to antidepressants.\cite{172,173} It could be therefore hypothesized that an increased inflammatory status might be responsible, at least in part, for this evidence.

Excitatory symptoms are twice as common in bipolar depression than in UD,\cite{165} and patients diagnosed with major depression that also show psychomotor agitation are nearly three times more likely to undergo mood-switching than depressed patients without excitatory symptoms.\cite{174} This is consistent with the theory that agitated depression should be re-conceptualized as an “attenuated mixed state” belonging to bipolar-spectrum disorders.\cite{171}

Until date, few studies have specifically focused on immune alterations during the bipolar depression. Higher levels of IL-1β, IL-2, IL-6, IL-8, IL-10, TNF-α, high-sensitivity CRP (hs-CRP), sIL-2R, sIL-6R, sTNF-R1, and IL-1Ra have been found in serum and/or plasma of depressed BD patients,\cite{79,81,100,178} although these findings were not completely confirmed in meta-analyses.\cite{69,70,84} Interestingly, some of these markers (i.e., sIL-R2, TNF-α, and sTNF-R1) appear to be elevated during manic/hypomanic phases as well.\cite{41} Depressed BD patients also show alterations in oxidative stress markers and glial activity.\cite{179}

Few studies have compared levels of inflammatory markers between BD and UD patients, and the results were mostly nonsignificant. However, a recent work from Bai et al.\cite{184} found that bipolar patients show higher serum levels of sIL-6R, CRP, sTNF-R1, and monocyte chemotactic protein-1 (MCP1) than patients with different subtypes of UD, hinting that dysregulation of the immune system is more severe in BD than in UD.

**Inflammation in BD prodromes**

Excitatory symptoms, although quite nonspecific, are also frequent during the prodromal stages of BD in adolescents.\cite{180} These symptoms include mood swings, hyperactivity, sleep disturbances, irritability and aggressiveness, and anxiety.\cite{181,182} Cytokines are thought to interact with adrenal and gonadal hormones during adolescence, therefore influencing neurodevelopment and contributing to subsequent onset of psychiatric diseases;\cite{183} a role for a preexisting pro-inflammatory status in adolescents with high-risk of developing BD has been suggested.\cite{184} Recently, a prospective study demonstrated alterations in the immune state, such as increased inflammatory gene expression in monocytes during adolescence and increased levels of chemokine ligand 2 (CCL2, also known as MCP1), a marker of monocyte activation and migration, during young adulthood in the offspring of BD patients.\cite{185}

**Inflammation in postpartum psychosis**

There’s a general consensus that postpartum psychosis may often occur as a first episode of BD.\cite{186,187} Pregnancy in itself is considered a period of great modifications in the function of the immune system and immune activation has been observed during the postpartum period.\cite{188,189} A recent study found reduced levels of T-cells, increased levels of monocytes, and increased expression of monocyte genes in patients with first-onset postpartum psychosis.\cite{190}
EFFECT OF PHARMACOLOGICAL TREATMENT ON INFLAMMATORY MARKERS IN BD

Mood stabilizing agents commonly used in the therapy of BD have been suggested to partially exert their activity via the regulation of the immune system and oxidative stress pathways.[191] A number of studies have provided evidence supporting anti-inflammatory effects of lithium via different mechanisms.[192,193] Lithium decreases the synthesis of pro-inflammatory enzymes and molecules (i.e. IL-1β, TNF-α, PG, NO, iNOS, COX-2 and PLA2), and regulates microglial activity in vitro.[194-198] Similarly, lithium therapy shows some immunoregulatory activity in bipolar patients. It has been demonstrated to decrease the number and the activity of inflammatory cytokine-producing cells in BD patients[197,200] and to reduce the synthesis of cytokines in vitro.[80,129,131,206-217] Anti-psychotic drugs such as clozapine, quetiapine, risperidone, and ziprasidone also show some immunoregulatory effect by modulating the AA signaling cascade, cytokine and acute-phase protein synthesis, and microglial activation both in vitro and in vivo.[80,119,131,206-217]

FUTURE DIRECTIONS

Because of the converging evidence pointing to inflammatory dysregulation in the pathophysiology of psychiatric diseases, drugs specifically modulating the inflammatory response, such as acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs (NSAIDs), omega-3 fatty acids, anti-TNF-α agents, minocycline, and N-acetyl cysteine (NAC) have been investigated as new therapeutic options, with still controversial results.[3,218-221] In particular, a randomized study proved the efficacy of adjunctive therapy with celecoxib, a nonsteroidal anti-inflammatory drug and a selective inhibitor of COX-2, in rapidly improving depressive symptoms in depression and mixed states of BD I and BD II patients.[222] Another study found elevated levels of gene transcripts for prostaglandin D synthetase and prostaglandin D2 11-ketoreductase during depressive episodes in rapid-cycling BD patients; add-on treatment with celecoxib improved the severity of both depressive and manic/hypomanic phases, although more pronounced benefits were noted during depression.[223]

Tumor necrosis factor-α has been suggested to play a major role in mechanisms related to inflammation, neurodegeneration, and possibly neuroprogression of the disease in BD. Another study by Guloksuz et al.[224] demonstrated a correlation between higher levels of TNF-α and a poor response to lithium treatment in BD patients. According to this evidence, TNF-α could be considered as a potential new target for the development of new drugs for BD therapy.[196,225] Antagonism of IL-6 has also been hypothesized to be a novel therapeutic option to improve clinical outcome in BD.[226]

CONCLUSION

The literature reviewed provides evidence for a role of the inflammatory system in the pathophysiology of mood disorders. Nevertheless, a high rate of variability is observed among the different studies, especially those focused on evaluating the peripheral expression of inflammatory markers. There is a general consensus that BD patients show higher levels of cytokines in blood samples compared to healthy controls; however, data are inconsistent and comparisons between peripheral levels of inflammatory markers in manic/hypomanic/mixed versus euthymic or depressed BD patients fail to converge to univocal conclusions. This may be explained by a number of reasons. First, studies differ in their methodology; some of them by assessing the expression of cytokines in serum, others in plasma, and yet others by evaluating cytokine production by in vitro stimulation of white blood cells from BD patients. Second, peripheral cytokine levels are influenced by several confounding factors, such as smoking status, body mass index, sleep disturbances, physical activity, and medications. Third, BD is highly heterogeneous in its manifestations so that a thorough selection of patients and classification of their mood state might be difficult. Finally, not all studies take into account factors such as age at onset and duration of illness, number of relapses, polarity of the last relapse, and the time intercurring from the last episode, which might be of importance in modifying the inflammatory status.

An enhanced pro-inflammatory status might partially explain the high rate of medical conditions often comorbid with BD, that is, cardiovascular, cerebrovascular, and metabolic diseases. Similarly, smoking, sleep impairment, and alcohol and substance abuse, the prevalence of which is high in BD patients, might contribute to the maintenance of a pro-inflammatory
milieu. It is known that chronic inflammation induces a number of negative consequences in the brain, such as a high rate of tissue damage and structural changes in several areas, which in turn underlie functional impairments in neurotransmission. These alterations underpin some kind of both neuroanatomical and neurophysiological “vulnerability” in BD and represent the biological substrate for further relapses and progression of the illness.

Clinical observations indicate that BD is, in fact, a progressive disease, with many recurrences leading to more and more frequent and severe relapses, and associated with a reduction of inter-episode duration time, cognitive decline, and a worsening of the response to treatment, both pharmacological and psychotherapeutic.[227–232] This ongoing process is likely to be exacerbated during acute phases of the illness, especially excitatory phases, and might be due, at least in part, to a stronger activation of the inflammatory system.[233,234] Drugs modulating the immune system, or specifically some of its components, currently represent a promising field of investigation toward the development of add-on therapies aimed to achieve better clinical outcomes in the treatment of BD.

Financial support and sponsorship
This study was part of the FIRB project code RBFR12LD0W_002 and has been funded by a grant of the Italian Ministry of Research.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
3. Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed moods: a review of the interactions between inflammation and mood disorders. Prog Neuropsychopharmacol Biol Psychiatry 2014;53;23-34.


100. Tsai SY, Chung KH, Huang SH, Chen PH, Lee HC, Kuo CJ. Persistent inflammation and its relationship to leptin and insulin in phases of bipolar disorder from acute depression to full remission. Bipolar Disord 2014;16:800-8.


114. Tsal MC, Huang TL. Thiobarbituric acid reactive substances (TBARS) is a state biomarker of oxidative stress in bipolar patients in a manic phase. *J Affect Disord* 2015;173:22-6.


