The inflammatory hypothesis of mood spectrum broadened to fibromyalgia and chronic fatigue syndrome

L. Dell’Osso¹, L. Bazzichi², S. Baroni¹, V. Falaschi¹, C. Conversano¹, C. Carmassi¹, D. Marazziti¹

ABSTRACT
Objective. The present paper is aimed at reviewing the literature data on the inflammatory hypothesis of mood spectrum, as well as the overlapping features with some chronic rheumatologic disorders, in particular fibromyalgia and chronic fatigue syndrome.

Methods. A literature search was carried out for English papers published in the years 2000–2014, using the following words: mood spectrum, depression, bipolar disorders, fibromyalgia, chronic fatigue syndrome, neurotransmitters, inflammation, neuroinflammation, cytokines.

Results. Overlapping features were highlighted between mood spectrum, fibromyalgia and chronic fatigue syndrome, suggesting common underlying mechanisms at pathophysiological level involving both the central nervous system and the immune systems.

Conclusion. Taken together, the literature would suggest that the borders between different medical domains should be reconsidered in the light of common processes linking them.

Introduction
Research in the field of neurobiology and psychopharmacology of depression focused mainly on monoamines, particularly on the serotonin (5-HT) system. Not surprisingly the development of second-generation antidepressants in the ‘80s was based on the study of drugs acting at the level of the 5-HT system, in particular on reuptake inhibition. However, since less than two thirds of depressed patients achieve full remission with the current antidepressants (1), other treatment targets have been explored. During the past decade, inflammation has been revisited as a possible aetiologic factor of mood disorders which has re-directed the field towards developing and/or re-purposing novel therapeutic options (2, 3). The relationship between mental health and inflammation was first noted in 1887 by Julius Wagner-Jauregg of the University of Vienna, Austria (4), but the link between inflammation and mood disorders was neglected for many years (5). The latest advancements in the neurobiological research are providing increasing evidence that inflammatory and neurodegenerative pathways would play a relevant role in the development of depression and mood disorders in general (6, 7). The inflammatory response may be appropriate, physiological and necessary in the presence of an infection, cellular damage or stress. Conversely, it may be inappropriate, pathological and damaging when it is reacting out of proportion to given stimuli, or reacting to the wrong stimuli, thus, causing undesired and unwarranted effects. There may be potentially detrimental effects of inflammation, regardless of the appropriateness of the response (8, 9).

One potential negative effect of inflammation is alterations in mood, sleep, energy, cognition, and motivation, all of which are part of mood disorder symptomatology.

Several inflammatory markers have been found in depressed patients including increased levels of acute phase proteins, pro-inflammatory cytokines and their receptors in peripheral blood and cerebrospinal fluid (CSF), lowered serum zinc, elevated peripheral blood concentrations of chemokines and prostaglandins (10–13). It has been reported that systemic inflammation may provoke a similar process in the central nervous system (CNS) a condition that has been labelled as “neuroinflammation”, through the activation of brain

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microglia (14). While in the case of brain injury or infection, microglial activation is necessary for host defense, a over-activation of microglia can trigger neurotoxic processes (15), as in the case of neurodegenerative diseases where a continuous and prolonged inflammatory response has negative effects (16). Pro-inflammatory cytokines have been found to pass the blood-brain barrier and reach the brain (17, 18), where they can activate both endothelial and immune cells, including perivascular macrophages that can produce further inflammatory mediators, and stimulate peripheral afferent nerves, including the vagus nerve, so that the cytokine signal may reach distant brain areas, including nucleus of the solitary tract and hypothalamus (17, 18).

Cytokine hypothesis of mood disorders

The cytokines and chemical factors produced during inflammatory response serve as excellent biomarkers when investigating the potential relationship between inflammation and mood disorders. Several investigators have taken this approach to repeatedly show an increased incidence of mood symptoms and mood episodes with elevated levels of inflammatory markers; notably, prostaglandin E2 (PGE2), acute phase reactant C-reactive protein (CRP), TNF-α, IL-1β, IL-2 and IL-6, in peripheral blood and CSF in major depressive disorder (MDD) (2, 19-22) and bipolar disorder (BD) (24-26).

Levels of pro-inflammatory cytokines like interleukin-1 (IL-1), IL-2, IL-4, IL-6 and tumour necrosis factor-α (TNF-α) are elevated during mania, while IL-6 is elevated during depression (26). Evidence of a stage-related impact on cytokines is suggested by the fact that pro-inflammatory cytokines IL-6 and TNF-α are elevated during both the early and late stage, while the anti-inflammatory IL-10 is increased only in the early phase of BD (27). Moderate increased levels of C-reactive protein (CRP), and in particular hsCRP, are highly correlated to manic episodes (28). In animals the administration of LPS or IL-6 may induce a behavioural syndrome that resembles depression and has been called sickness syndrome characterised by anhedonia, anorexia, sedation, behavioural disturbances, decreased locomotor activity and exploration, and which shows strong similarity with depression (29).

In humans, the administration of LPS to healthy volunteers was found to cause an acute increase of depressive and anxious symptoms (30), whereas the administration of Salmonella typhi vaccine, a cytokine inducer, to healthy subjects provoked mood depression, fatigue, psychomotor retardation and cognitive disturbances (31, 32). Moreover, it has been recently proposed that depression could be characterised by an increased translocation of LPS from intestinal gram-negative bacteria, a condition called leaky gut which might induce peripheral inflammation (33, 34).

Long-term exposure to cytokines may precipitate the onset of depression: 70% of subjects who underwent immune-therapy with INF-α for infection or cancer, develop a full blown depression (35-39). The cytokine hypothesis of depression is also supported by the evidence of high comorbidity rates of depression with inflammatory diseases, including coronary heart disorder, asthma, allergies, human immunodeficiency virus (HIV) infection, diabetes, obesity, metabolic syndrome (40, 41). Autoimmune disorders such as psoriasis, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus provide an excellent model of a heightened inflammatory state. This observation of increased mood disorders in more benign inflammatory conditions is important as it suggests that mood symptoms associated with medical comorbidities are not simply ‘feeling bad about having a terrible disease’ but may have a more biologic nature to the sickness behaviour, i.e. the inflammatory-mood pathway.

Furthermore, the high incidence of depression in the post-partum period might be related to the significant inflammatory activity which characterises this phase, including increases in IL-6 and lower plasma tryptophan (TRP) with indolamine 2,3 dioxygenase (IDO) activation (42).

In humans, the efficacy of antidepressants was shown to be increased by adding anti-inflammatory drugs. Acetylsalicylic acid augmentation was shown to accelerate antidepressant efficacy of fluoxetine in depressed patients (43), celecoxib, a cyclooxygenase-2 inhibitor, in combination with reboxetine led to a clinical improvement (44), TNF-α antagonist, provoked a significant improvement of depression (45). ω3 poly-unsaturated fatty acids (PUFAs), have relevant anti-inflammatory effects (46): individuals with lower serum ω3 PUFA or higher ω6/ω3 ratio showed significantly higher stress-induced TNF-α and INFγ responses, which, in turn, were related to anxiety and perceived-stress levels (47, 48). Antidepressants seem to have anti-inflammatory effects, since they were demonstrated to reduce INF-γ and increase IL-10 concentrations (49). A recent meta-analysis reported that antidepressant treatment can reduce IL-1β and IL-6 serum levels but not those of TNF-α (50-51). In particular, SRIs seemed to be able to reduce levels of IL-6 and TNF-α, while other antidepressants, although effective on depressive symptoms, did not appear to reduce cytokine serum levels.

Cytokines and inflammatory cascade

Cytokines, more specifically IL-2 and IFN through stimulation of inflammatory signalling pathways, such as nuclear factor (NF) κB, p38 mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription (STAT) 1 and 3, can activate the enzyme indoleamine 2,3 dioxygenase (IDO) (52) that induces the degradation of tryptophan (TRP) into TRP catabolites along the IDO pathway (TRYCATs), such as kynurenine (KYN) (53, 54). It is also hypothesised that the activation of the molecular signalling inflammatory pathways might be responsible for the lowered central 5-HT concentration found in depression. TRYCATs seem to display neurotoxic effects. In particular, at the level of microglia, KYN is converted into quinolinic acid (QA), that exerts its neurotoxicity by inducing oxidative stress (OS) resulting in lipid peroxidation, through the activa-
tion of N-methyl-D-aspartate (NMDA) glutamate receptors (55-58).

A modification of the 5-HT hypothesis of depression has been proposed focusing on inflammation-induced TRP degradation and TRYPATs production rather than on TRP and 5-HT depletion (7). Indeed, after IDO activation more TRP would be converted into TRYPATs, with a decrease of both 5-HT and TRP and increased neurotoxicity. IL-6 and TNF-α have been shown to increase the breakdown of 5-HT through facilitating the conversion of 5-HT to 5-hydroxyindolacetic acid (5-HIAA) (59, 60).

More recently, it has been proposed another link between inflammatory pathways and 5-HT. In particular autoimmune reactions directed against 5-HT has been observed in 109 depressed patients, as compared with healthy control subjects (61). There was also a positive strong association between the autoimmune response against 5-HT and inflammatory pathways, as patients with positive 5-HT antibodies showed increased serum neopterin and lysozyme, and increased plasma TNFα and IL-1.

Cytokines have been also demonstrated to produce several effects at the level of the hypothalamus-pituitary-adrenal (HPA) axis. Replicated studies have demonstrated that cytokines such as IL-1, IL-6, TNF-α and IFN-α activate the HPA axis, through the expression and release of corticotrophin-releasing hormone (CRH) (62, 63), adrenocorticotropic hormone (ACTH) and cortisol (64, 65). HPA axis that normally inhibits the inflammatory signalling pathways including NFkB, in pathological conditions would lose this inhibitory action. In depression, glucocorticoids seem to lose their ability to work upon the immune cells, while inhibiting a further release of pro-inflammatory cytokines, adhesion molecules and acute phase proteins (9). During depression or in condition of chronic stress, glucocorticoids cannot reduce anymore the inflammatory pathways activation and suppress the further release of cortisol. This condition, known as glucocorticoid resistance, seems to be, at least in part, related to the action of cytokine on GRs, and would lead to the perpetuation of the central inflammation and of the activation of the HPA axis (9). In depressed patients, significant and positive correlations between IL-6 activity and post-Dexamethasone cortisol values were found (62). The cytokines-mediated activation of the inflammatory signalling molecules, such as NF-κB, p38 MAPK and STAT, was found to limit GRs function through the impairment of the translocation from cytoplasm to nucleus and the inhibition of GRs binding to DNA (66). Cytokines seem to alter GR expression by increasing the production of GRβ, a less active GR isoform, and by reducing the α isoform expression, which is the active form of GR (66). Further it has been shown that cortisol increases hepatic tryptophan 2,3-dioxigenase (TDO) activity, a potent catabolic enzyme of TRP, therefore leading to TRP depletion and increased levels of KYN, kynureninic acid and QA (67-69).

When depression occurs in the context of a medical illness, such as autoimmune or inflammatory diseases, infectious or tissue damage or destruction, the activation of peripheral and, then, central inflammatory responses can be easily attributed to the same factors leading to the somatic illness. Karl Abraham (1911) proposed the role of stress critical for the onset of psycho-pathology. The occurrence of negative events during early childhood was essential to the development of depression and recent events of loss would provoke the onset of melancholia (70). Psychosocial stressors have been found to activate peripheral and central inflammatory responses (71-74). Maes et al., (47, 75) first demonstrated that psychological stress may induce an inflammatory response with increased levels of INFγ and TNF-α. Chronic stress was associated with increases of PCR and IL-6 (72-74). Stress may lead to the activation of the inflammatory response involving catecholamines and the HPA axis system (9) with release of CRH and catecholamines. Pro-inflammatory cytokines would enter the brain and, once reached the microglia, activate the inflammatory signalling pathways, such as NFkB, causing a central neu-
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Fibromyalgia is characterised by chronic widespread debilitating musculoskeletal pain, increased pain sensitivity including allodynia and hyperalgesia with tenderness but no structural pathology in muscles, ligaments, or joints and stiffness throughout the body (105, 106). Patients with fibromyalgia complain of fatigue, sleep disturbances, anxiety, depression, cognitive concentration, and memory dysfunction, and tenderness at 11 or more of 18 designated “trigger points” where ligaments, tendons, and muscle attach to bone (107-111). The prevalence of fibromyalgia has been estimated to be about 2.0% of the general population, and seven times more common in women than in men (112, 105). The prevalence increases with age, with highest values attained between 60 and 70 years where it can exceed 7% of the general population in women. Fibromyalgia significantly impairs function, increases work absenteeism and general healthcare use and results in a profound deterioration of the quality of life of patients (113-115). There is no known cause, although the condition may occur following viral infections, exposure to toxins, or physical or emotional trauma (116). The pathophysiology of fibromyalgia is not related to peripheral musculoskeletal changes, but to abnormalities of the central pain processing mechanisms (117) which result in central pain sensitisation (118-120) and to abnormalities in the HPA axis. Pain perception is a complex bidirectional process of ascending and descending pathways. Noceptive input from peripheral afferent neurons passes via the dorsal horn of the spinal cord to the higher brain centers involved in pain perception. Descending inhibitory projections to the spinal cord attenuate the nociceptive input. The neurotransmitters involved in this process are the same as those which regulate mood, sleep regulation and cognitive functions providing a neurochemical rationale for the wide range of symptoms seen in fibromyalgia. Is has been hypnotised to represent abnormal sensory processing at NMDA glutamate receptor-mediated neurotransmission in unmyelinated fibres which carry pain impulses. It has also been hypothesised as abnormal substance P mediated neurotransmission. Attenuation of hypersensitive central neurons through ligands acting at the a2-d subunits of voltage-dependent calcium channels and increased noradrenergic and serotonin activity of the descending inhibitory pathways are two mechanism that are currently exploited by recent medication for the treatment of fibromyalgia (121, 122). Neurochemical mechanisms involving the serotonergic and noradrenergic pathways have been postulated to be a possible common denominator between pain and depression. Most of those diagnosed with fibromyalgia have a comorbid mood or anxiety disorders. If pain and depression share a common psychopharmacology, drugs acting on the serotonergic and noradrenergic systems, such as dual action antidepressants, would be expected not only to improve mood and other psychological symptoms of depression, but also to improve physical symptoms such as chronic pain (123-127).

Sickness behaviour (128) is a set of behavioural and physiological changes that patients show during the course of an infection; these are considered to be adaptive responses designed to maintain homeostasis during infection. It has been demonstrated that the behavioural changes are due to the effects of pro-inflammatory cytokines on brain cellular targets. Upon stimulation, the immune system secretes pro-inflammatory cytokines that convey a message to the brain and re-organise behavioural priorities. The systemic or central injection of IL-1β, IL-6 and TNF-α in animals has been shown to induce sickness behaviour (129). Since FM patients refer some symptoms similar to those of sickness behaviour, regarding physiological and emotional changes, it has been hypothesised that cytokines might play a role in linking the immune and the neural systems in FM.
Elevation of cytokines has been reported in fibromyalgia (130-132). One of the main symptoms of inflammation is pain, which is also a primary symptom of FM. Evidence has shown that cytokines are involved in the generation of generalised pain and hyperalgesia in inflammatory and neuropathic conditions. Chronic sub-inflammation and an impaired response of the immune system to stressors may be present in FM. The recent theory that cytokines transmit messages from the periphery to the brain by means of humoral and neural pathways may explain the mood disorders (anxiety, depression) observed in FM patients (133-135). Studies have linked the activation of this system to the mood disorders observed in patients suffering from chronic inflammatory disorders including autoimmune disease, coronary heart disease and asthma (136), as well as in patients with psychiatric disorders (137-139). One study (140) revealed higher levels of IL-10 and IL-8 in all FM patients, irrespective of the presence or absence of psychiatric disturbances, compared to controls. The cytokine pattern in FM patients with psychiatric symptoms is similar to that of FM patients taken as a whole. The study shows the presence of a mechanism of sub-inflammation activated by increased IL-8 levels in FM patients and confirmed by consensual feedback, the negative production of IL-10, and by the correlation with rheumatological clinical features. In a study rare missense variants of the *MEFV* gene were found in 15% of the patients with FM which had higher levels of IL-1B compared to controls (141). Elevation in inflammatory activity may be a widespread phenomenon in FM, given a study that reported TNF-alpha, IL-1 and IL-6 in the majority of FM patients but in none of the controls (142). Elevation of IL-8 appears to be one of the more consistent findings in FM (143, 131, 144).

**Conclusion**

Increasing data continue to support the notion that nerves and immune systems interact through different messengers, such as classical neurotransmitters, cytokines and neuropeptides. Indeed, neurotransmitters and neuropeptides can be released, and in some cases synthesised, at inflammatory sites and, as such, they may influence the activity of cells belonging to the immune system (145-147). In addition, it has been demonstrated that cytokines may trigger neurotoxic effects, modulate neuropeptide receptors and reduce the availability of those amino acids precursors of neurotransmitters. The inflammatory and neurodegenerative hypothesis of depression postulates that both psychosocial and/or somatic stressors may play a role in mood disorders through inflammatory processes. Preclinical and clinical studies of depression have reported an increased production of pro-inflammatory cytokines, including interleukin-1beta, IL-6, tumour necrosis factor and interferon, as well as oxygen radical damage and increased catabolism of TRP to neurotoxic TRP catabolites. Moreover, the most part of antidepressants seem to have anti-inflammatory effects, while anti-inflammatory drugs may augment the clinical efficacy of antidepressants. The overlapping symptoms and immunological alterations shared by mood spectrum and chronic rheumatological disorders, such as fibromyalgia and chronic fatigue, suggest that inflammatory processes can be the common bases of disorders belonging to different domains (148, 149). Conversely, they suggest that different disorders may be more closely related than previously supposed.

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