

# Are Mood and Anxiety Disorders Inflammatory Diseases?

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## ABSTRACT

In the last few decades there has been a growing interest in the role of psychoneuroimmunological dysfunction in neuropsychiatric disorders. This article presents recent advances in the literature, from pre-clinical and clinical studies, suggesting that mood and anxiety disorders are, at least in part, conditions in which the inflammatory system is activated. The evidence-base comprises alterations in the peripheral immune systems of patients with mood or anxiety disorders, together with the development of depression- and anxiety-like symptoms induced by inflammatory agents. The reported anti-inflammatory effects of current psychotropic medications as well as the efficacy of anti-inflammatory medications in treating symptoms of depression and anxiety are also reviewed. Finally, potential mechanisms mediating the link between inflammation and symptomatology presented in these neuropsychiatric illnesses are discussed as well. [*Psychiatr Ann.* 2015;45(5):240-248.]



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Gaining momentum in recent years, contemporary research has uncovered substantial evidence to suggest that dysregulation of the immune system, and more specifically a low-grade inflammation, is involved in the pathogenesis and maintenance of several neuropsychiatric conditions. Although depression has taken center stage in the field of mental health, researchers have begun to explore potential avenues that implicate such dysregulation in the complex interactions that underpin anxiety disorders, commonly found as a comorbid condition alongside depression, as well as bipolar disorder (BP).<sup>1</sup> The immune system itself is comprised of numerous components and pathways, conventionally divided into two branches—the innate and the adaptive systems—with the primary objective to eliminate or to prevent entry of foreign or infective agents (see article by Beurel, this issue). A mechanism of particular interest in this context is the inflammatory response, whereby secreted cytokines key signaling molecules and activate the peripheral innate immune cells as well as induce behavioral changes that are evolutionary in the fight against such foreign and infective agents. This so called “sickness behavior” is characterized by cognitive impairment, lethargy, and alterations in mood and appetite, all of which resemble aspects of depressive- and anxiety-related behavior.<sup>2</sup> Thus, it is plausible that chronic activation of the immune system, as proposed to occur in at least some individuals with mood or anxiety disorder, results in prolonged sickness behaviors, which in turn plays a role in the onset and perpetuation of these symptoms.<sup>3</sup> Support for mood and anxiety disorders as conditions with an inflammatory component also comes from the increasingly high prevalence of depression in those with infectious and autoimmune conditions as well as research connecting inflammatory medical conditions with the subsequent

development of mental illness.<sup>4,5</sup> Moreover, largely dominating the literature is amassing evidence revealing elevated levels of inflammatory markers in the peripheral blood and cerebral spinal fluid (CSF) of individuals suffering from depression, BD, and other anxiety disorders when compared to healthy subjects.<sup>6</sup>

In this article, the authors review the above-mentioned evidence showing altered levels of inflammatory markers in mood and anxiety disorders. Also discussed are the potential immune-regulatory effects of treatments for mood and anxiety disorders that may contribute to the efficacy and the novel use of anti-inflammatory agents in treating these disorders. A brief summary of the pathophysiological changes that occur during an inflammatory state and how that may be mechanistically relevant in mediating this association is also explored.

#### **EVIDENCE FOR ELEVATED INFLAMMATORY MARKERS IN MOOD AND ANXIETY DISORDERS**

Many methods have been used to determine the extent of inflammation in research; however, the measurement of peripheral blood levels of cytokines and of the acute-phase protein, C-reactive protein (CRP), have been the most described in literature relating to mood and anxiety disorders. Cytokines are key signaling proteins that coordinate and liaise between both branches of the immune system, regulating the differentiation, proliferation, and function of immune cells. Moreover, some cytokines can directly translate changes in peripheral immune function to the brain via activation of microglia cells, thus underpinning the affective and cognitive symptomatology documented in those with immune dysfunction.<sup>7</sup> CRP is produced by the liver in response to immune activation as it facilitates the fight against bacteria; most importantly, its levels are considered a clinically significant

marker of inflammation, with accepted cut-off values indicating mild, moderate, and severe inflammation.<sup>8</sup> Studies on cytokines and CRP in mood and anxiety disorders form the basis of the evidence that informs the majority of this discussion here (Table 1).

With regards to depression, data obtained in a recent meta-analysis of longitudinal studies regarding the cytokine interleukin (IL)-6 and CRP provide support for a role for inflammation in the pathogenesis of this disorder. With a large sample of participants numbering in the thousands, the authors found a significant association between elevated CRP and subsequent onset of depressive symptoms (and a weaker association between IL-6 concentrations and subsequent symptoms), suggesting a causative link between increased inflammation and depression.<sup>9</sup> Other meta-analyses reinforce this relationship, finding elevated levels of IL-6 and CRP, and also of the other immune markers, IL-1 and tumor necrosis factor (TNF)-alpha, in both serum and plasma of patients with major depressive disorder.<sup>10,11</sup> A dose-response relationship between cytokine concentration and severity of symptoms has also been proposed, based on the evidence supporting a continuum between community-based and clinical samples in the levels of proinflammatory cytokines.<sup>11</sup> Although findings relating to IL-6 and TNF-alpha have been relatively consistent, the picture for other markers is less clear. A meta-analysis found no differences in IL-1 beta, IL-4, IL-2, IL-8, IL-10, or interferon (IFN)-gamma between patients with major depression and the controls.<sup>10</sup>

A similar pattern can be seen in the literature for BD. An earlier systematic review reported elevated concentrations of IL-6, TNF-alpha, CRP, and soluble IL-2 receptor (sIL-2R) levels in the peripheral blood of those diagnosed with BD compared with healthy controls.<sup>12</sup> A more recent meta-analysis similarly

TABLE 1

## A Summary of the Main Findings

Disorder	Type	Study	CRP	IL-1	IL-1 beta	IL-1RA	IL-2	sIL-2R	IL-4	IL-6	sIL-6R	IL-8	IL-10	TNF-alpha	sTNF-R1	IFN-gamma	CXCL8	CXCL3
Depressive symptoms	Meta-analysis	Valkanova et al. <sup>9</sup>	↑							↑*								
Major depressive disorder	Meta-analysis	Dowlati et al. <sup>10</sup>			=		=	=	↑		=	=	↑		=			
	Meta-analysis	Howren et al. <sup>11</sup>	↑	↑		=			↑									
Bipolar disorder	Systematic review	Goldstein et al. <sup>12</sup>	↑					↑	=	↑		↑	=	↑				
	Meta-analysis	Modabbernia et al. <sup>13</sup>			↑*	↑	=	↑	↑	↑*	↑	=	↑	↑	↑	=		
	Systematic review	Munkholm et al. <sup>14</sup>		=	=	=	=	↑	↑	=	↑	=	=	↑	↑	=		

↑ indicates significantly elevated levels; ↓ indicates significantly decreased levels; = indicates no significant difference; \* indicates significant difference after adjusting for confounding variables.

CRP = C-reactive protein; IL = interleukin; IL-1RA = interleukin-1 receptor antagonist; sIL = soluble; IFN = interferon; TNF = tumor necrosis factor; CXCL = chemokine.

↑\* indicates significantly elevated levels after adjusting for confounding variables.

↓\* indicates significantly decreased levels after adjusting for confounding variables.

↑\* indicates significantly elevated levels after adjusting for confounding variables.

found significantly elevated levels of TNF-alpha and sIL-2R, along with IL-4, IL-10, sIL-6R, soluble TNF-R1, and IL-1 receptor antagonist, whereas levels of IL-6 and IL-1 beta tended to be non-significantly higher.<sup>13</sup> A weaker association between IL-6 and BD was replicated in a recently published systematic review.<sup>14</sup> Furthermore, results for other cytokines are even less consistent, ie, IL-2, IL-1 beta, and IFN-gamma, as well as anti-inflammatory cytokines IL-4 and IL-10.<sup>12</sup>

Anxiety research has mostly provided similar results to those described for mood disorders, although comparative evidence is relatively sparse. To date, the focus has been on posttraumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD), and study results are discussed here. A recent review reported the presence of high lev-

els of IL-1 beta, IL-6, TNF-alpha, and CRP in the blood of patients diagnosed as having PTSD as compared to healthy controls.<sup>15</sup> Levels of IL-6 and TNF-alpha were also found to be higher in women with PTSD versus women in a nonclinical "traumatized" sample, suggesting a specificity of such inflammation to the clinical diagnosis.<sup>16</sup> Interestingly, although one study found no difference in plasma levels of these markers, evidence for a heightened inflammatory state was found after observing increased spontaneous *ex vivo* production of IL-1 beta, IL-6, and TNF-alpha by peripheral blood mononuclear cells (PBMCs) in participants with PTSD.<sup>17</sup> Furthermore, the production of IL-6 and TNF-alpha was significantly correlated with the severity of symptoms.<sup>17</sup> Patients were observed to have higher levels of CRP than the controls,

even after adjusting for a wide range of confounding variables relating to sociodemographics, lifestyle, anthropometric, metabolic, and medical factors; the same conclusion was also supported by results from a similar study controlling for comorbid depression.<sup>18,19</sup>

Furthermore, a longitudinal study of plasma CRP levels in Marines, pre- and post-deployment, who were dispatched to warzones showed a greater vulnerability of developing PTSD symptoms in those whose baseline CRP levels were elevated.<sup>20</sup> However, contradictory evidence in a large-scale population-based study found no association between CRP and PTSD.<sup>21</sup> In another PBMCs study, the authors examined nuclear factor-kappaB pathway activity—a molecular signaling pathway involved in the regulation of inflammation—and found it to be heightened in women with childhood

TABLE 1. (continued)

## A Summary of the Main Findings

Disorder	Type	Study	CRP	IL-1	IL-1 beta	IL-1RA	IL-2	sIL-2R	IL-4	IL-6	sIL-6R	IL-8	IL-10	TNF-alpha	sTNF-R1	IFN-gamma	CXCL8	CXCL3
PTSD	Narrative review	Pace et al. <sup>15</sup>	↑		↑					↑				↑				
	Study	Gill et al. <sup>16c</sup>			=					↑				↑				
	Study	Gola et al. <sup>17</sup>			↑ <sup>b</sup>					↑ <sup>b</sup> / =		=	=	↑ <sup>b</sup> / =				
	Study	Heath et al. <sup>18</sup>	↑															
	Study	Spitzer et al. <sup>19</sup>	↑															
	Study	Eraly et al. <sup>20e</sup>	↑															
	Study	Baumert et al. <sup>21</sup>	=															
OCD	Systematic review	Gray et al. <sup>23</sup>			↓					=				=				
	Study	Fontenelle et al. <sup>24</sup>													↑		↑	↑
Anxiety disorders	Study	Vogelzangs et al. <sup>25d</sup>	↑							=				=				
	Study	Janelidze et al. <sup>26</sup>										↓						

abuse-related PTSD versus healthy controls, and also positively correlated with the severity of symptoms.<sup>22</sup>

With regards to OCD, an earlier review concluded that cytokine concentrations in OCD was inconclusive, reporting contradictory findings for IL-6 and TNF- $\alpha$ .<sup>23</sup> However, a more recent study reports evidence for a low-grade inflammation in OCD, observing a significant increase in chemokines CXCL8 and CCL3 along with increases in sTNF-R1.<sup>24</sup>

Research on the other anxiety disorders is noticeably limited, although initial efforts are detailed here. A large adult cohort study examined associations between plasma concentrations of CRP, IL-6, and TNF-alpha with types and characteristics of the anxiety disorder. After sociodemographic and lifestyle factors, and the presence of cardiovascular disorders, diabetes, and chronic medical conditions were taken into account, findings suggested that levels of CRP were significantly elevated only

in men experiencing a current anxiety disorder.<sup>25</sup> Studies have also investigated associations between suicide risk, anxiety disorders, and levels of immune dysregulation, reporting lower levels of central and peripheral IL-8 in suicide attempters with anxiety when compared to healthy controls, which shows a significant negative correlation between symptoms of anxiety and plasma and CSF IL-8 concentrations. Furthermore, a genetic component was suggested after individuals found to possess the IL-8

251T allele, associated with lower IL-8 production than the -251A variant, presented with more severe levels of anxiety.<sup>26</sup>

IL-6 and TNF-alpha appear to be the more consistently raised markers across disorders. However, results should be interpreted with caution, especially considering the heterogeneity of the findings. In depression, moderators such as age have been suggested to account for the heterogeneity in cytokine levels measured among individuals with depression.<sup>27</sup> A lack of homogeneity in the study methods and measurement protocols in recording and controlling for clinical and environmental factors—ie, body mass index, medications, gender, and lifestyle factors—may contribute to the disparity of the data.<sup>11</sup>

#### INDUCTION OF SYMPTOMS BY INFLAMMATORY AGENTS

Further support for a role of inflammation in the pathogenesis of mood and anxiety disorders can be found in studies reporting depressogenic and anxiogenic effects of proinflammatory agents. Lipopolysaccharide endotoxin (LPS) is part of a gram-negative bacteria outer cell membrane, and as such is recognized by toll-like receptors (TLR) on phagocytic cells as foreign. A significant immune response is elicited and cascade of cytokine expression is induced, primarily resulting in elevated concentrations of IL-beta, IL-6, and TNF-alpha.<sup>28</sup> Studies in rats have observed a set of depressive-like behaviors persisting beyond the initial sickness-behaviors, marked by a significant decline of mobility in a forced-swim and tail suspension test, likened to hopelessness, as well as a disinterest in sweetened solution, likened to anhedonia, after administration of LPS.<sup>29</sup> Further studies in the same animal model also observed anxiety-like behavior alongside anhedonia.<sup>30</sup> Interestingly, LPS-induced anxiety-like behavior in rodents is reversed by subse-

quent treatment with etanercept, a TNF-alpha antagonist and anti-inflammatory medication.<sup>31</sup> Research in humans has also demonstrated a dose-response relationship between the dose of LPS administered, and subsequent elevations

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of proinflammatory cytokines IL-6, IL-10, IL-1Ra, and TNF-alpha, as well as subsequent increases in negative mood, anxiety, and cognitive impairment.<sup>32</sup>

Similar observations can be extrapolated from prospective studies of the therapeutic administration of cytokines in humans. For example, IFN-alpha for chronic hepatitis C virus infection is known to upregulate production of IL-6, leading to an increase in peripheral and CSF IL-6 concentrations.<sup>33</sup> It is suggested that this upsurge is responsible for the depressive symptomology that affects up to 30% of individuals undergoing such treatments.<sup>34</sup> Alongside depression, a range of other side effects are induced, notably anxiety and in some cases mania characterized by hyper-agitation and irritability, or less often euphoria.<sup>35</sup> Indeed, adjunctive use of antidepressant medications, either prophylactically or initiated during treatment, are often used to manage such neuropsychiatric symptoms,<sup>36</sup> whereas major depressive and manic episodes are cause for treatment cessation.<sup>35</sup>

#### ANTI-INFLAMMATORY ACTION OF CURRENT PSYCHOTROPIC AGENTS

Investigations of psychotropic drugs also reveal immunoregulatory effects, and such an action may contribute to their efficacy. Evidence from

*in vitro* and *ex vivo* studies has shown that antidepressant medication, most notably selective serotonin reuptake inhibitors (SSRIs), decreases production of proinflammatory markers, such as TNF-alpha, while increasing anti-inflammatory cytokines like IL-10.<sup>37</sup> Additionally, the expression of inflammatory genes has also been examined in association with antidepressant use: transcription of both IL-1 beta and IL-6 has been observed to be lower after treatment with such medication, although interestingly only the latter was linked with treatment response.<sup>38</sup> The most common therapeutic treatment for BD—lithium—has also been recognized for its regulatory effects on inflammatory markers; abnormal cytokine production, associated with BD, has been recorded to decrease after therapeutic administration of lithium, and fewer patients who are treated with it show a persistent elevation of CRP levels.<sup>39,40</sup> Finally, animal research has uncovered anti-inflammatory effects of benzodiazepines, frequently prescribed as an anxiolytic treatment; derivatives of the class produced a significant decrease in the production of IL-6, inferring anti-inflammatory effects.<sup>41</sup>

#### NOVEL USE OF ANTI-INFLAMMATORY AGENTS

Although work in this field is only in the initial stages, several studies already appear to be producing promising findings, showing reduction of symptoms after treatment with an anti-inflammatory drug<sup>42</sup> (for a more complete review and discussion of the literature on whether anti-inflammatory agents are antidepressants, see the review by Raison and Miller, this issue). Earlier studies in patients with inflammatory conditions, such as psoriasis, revealed an unexpected improvement in depressive symptoms, independent of an improvement in the conditions for

which they were prescribed.<sup>43,44</sup> More recently, adjunctive anti-inflammatory medications have been examined for their effects on mood and anxiety symptoms in patients with a primary neuropsychiatric diagnoses. Minocycline is a second-generation tetracycline able to cross the blood-brain barrier, with a complex mechanism of action including inhibition of cytokine secretion and cyclooxygenase (COX)-2 expression, with some promising results for OCD, BD, and depression, at least for subgroups of patients.<sup>45</sup> Acetyl-salicylic acid, the active component in aspirin, is a COX-1 and COX-2 inhibitor; studies of its use as an adjunctive to preexisting psychotropic drugs revealed beneficial results versus monotherapy when combined with lithium, fluoxetine, and other SSRIs.<sup>46-48</sup> For celecoxib, another COX-2 inhibitor, significant reductions were observed in depressive symptoms in participants after the combined treatment with reboxetine.<sup>49</sup> A randomized control trial (RCT) of the adjunctive use of celecoxib for BD also found that depressive symptoms began to subside after only 1 week of treatment when accompanied by a mood stabilizer or atypical antipsychotics.<sup>50</sup> Support is accumulating too for the use of supplementary omega-3 fatty acids, which have anti-inflammatory components, and have been shown to have antidepressant and anxiolytic properties, although results have been mixed. A recent placebo-controlled study confirmed anti-inflammatory effects, characterized by a reduction in LPS-induced IL-6 production, and observed a concomitant anxiolytic effect with significant reductions in symptomatology<sup>51</sup>; however, in a small trial in OCD patients, there was no benefit.<sup>52</sup> The omega-3 fatty acid has also proved effective as a mood stabilizer in BD, although a more recent meta-analysis concluded it to be effective only for depression and not for mania.<sup>53,54</sup> Eicosapentaenoic acid specifically is effective in preventing IFN-alpha-in-

duced depression.<sup>55</sup> Of note, an RCT of infliximab, a TNF-alpha antagonist, in treatment-refractory depression patients revealed no difference from placebo in the overall sample, although there was some benefit in a subgroup of patients with higher baseline inflammation as measured by CRP level of >5 mg/L.<sup>56</sup> Therefore, prediction of the success of such agents for the treatment of anxiety or depression might be related to baseline immune conditions.

### EFFECTS OF CYTOKINE ON THE BRAIN

Although the accumulation of evidence presented here appears only to confirm an association between immune activation and mood and anxiety disorders, evidence for the mechanisms by which cytokines have an effect on the brain provides support for how immune activation might contribute to these behavioral symptoms. Although these mechanisms are still under investigation, a bidirectional relationship between the peripheral immune system and the brain has been established.<sup>57</sup>

Contrary to earlier beliefs, it is now known that brain constituents—neurons, microglia, and astrocytes—can produce and express cytokines and their respective receptors as well as influence peripheral cytokine signaling. Moreover, cytokines can regulate behavior by affecting neurotransmitter and neuroendocrine function and neural plasticity.<sup>58</sup>

Cytokines affect the synthesis, release, and reuptake of all neurotransmitters linked to the development and maintenance of affective disorders.<sup>59</sup> For example, IFN-alpha attenuates the expression of the serotonin receptor 5HT1A,<sup>60</sup> and patients treated with the cytokine have lower levels of serum serotonin, particularly those who develop depression.<sup>61</sup> Notably, the severity of depression in IFN-alpha-treated patients has been correlated with lower

levels of the serotonin metabolite 5-hydroxyindoleacetic acid, indicating reduced brain serotonergic activity.<sup>62</sup> Another pathway affecting serotonergic neurotransmission is the tryptophan pathway: more specifically the activation of enzyme indoleamine 2,3 dioxygenase (IDO) that occurs in inflammatory states. IDO converts tryptophan—precursor of serotonin—into kynurenine (KYN) and its downstream metabolites quinolinic acid and kynurenic acid. Depressive-like behavior has been observed in mice after administering KYN,<sup>63</sup> although the therapeutic effects of an IDO inhibitor pretreatment on subsequent LPS-induced anxiety-like behaviors in mice have also been demonstrated.<sup>30</sup> Indeed, a shift in the tryptophan-KYN ratio, reducing serotonin availability, has been implicated in inflammation-induced depression,<sup>62</sup> whereas decreased tryptophan levels have also been seen in BD patients in the manic phase.<sup>64</sup> With regards to dopamine, inflammation is linked with a reduction in the activity of the dopaminergic system. IFN-alpha-induced symptoms in both rats and primates have been associated with reduced concentrations of dopamine and homovanillic acid—one of its metabolites.<sup>65,66</sup> Moreover, an increase in norepinephrine in the brain has been observed after peripheral and central administration of IL-1 and TNF-alpha.<sup>67</sup>

Also important is the effect of cytokines on the hypothalamic-pituitary-adrenal (HPA) axis, a key neuroendocrine system and one often implicated in the pathogenesis of mental health disorders. Cytokines can activate the HPA axis both directly and by suppressing the functioning of the glucocorticoid receptors (GR), a key transcription factor that keeps HPA axis activity under control through a negative feedback loop activated by the main HPA axis hormone—cortisol.<sup>68</sup> Indeed, clinical studies of patients have revealed altered GR func-

tion in depression, BD, and PTSD.<sup>68-70</sup> Unfortunately, despite the link between inflammation and HPA axis activity, and dysfunction of each system in those with mental illness being described in recent years, few studies have examined both concurrently.<sup>71</sup> A recent postmortem study in psychosis used gene-expression techniques to identify a pattern of expression of a range of inflammatory/GR-related genes in the brain indicative of “high-inflammation/stress,” which may be common across schizophrenia and BD. They found that patients with schizophrenia and BD were more likely to fall into this group as opposed to the “low-inflammation/stress” group; thus providing evidence for concomitant alterations in both stress and inflammatory signaling, suggesting that elevated glucocorticoids decrease GR function and subsequently disrupting the natural inhibition of the immune system.<sup>72</sup> Another earlier study examined the proinflammatory cytokine macrophage inhibitory factor (MIF),<sup>73</sup> which acts to desensitize immune cells to the anti-inflammatory effects of GC. It was found that MIF was higher in those participants with higher depression scores, and was associated with a smaller cortisol response to an acute social stressor and lower morning cortisol.<sup>73</sup> Furthermore, a study examining LPS-induced behavioral changes found that in patients administered a low dose of the endotoxin, mood changes were negatively correlated with changes in plasma cortisol, although the same association was not found with the high dose even though strong associations between circulating IL-6 and increases in negative mood were observed.<sup>32</sup> These findings suggest an association between inflammation-induced mood changes and HPA-axis function only with a low-grade inflammation, characteristic of the level of inflammation observed in those with mood and anxiety disorders. Finally, another biomarker of relevant HPA function is the level of adrenocorticotro-

phic hormone, with elevated levels indicating an exaggerated HPA response. Elevated levels of the hormone have been found to predict IFN- $\alpha$ -induced depression in humans, and to be associated with depressive-like behavior in monkeys.<sup>65,74</sup> Such findings are thought

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to be due to an increased sensitivity of corticotrophin-releasing hormone pathways in these individuals, conferring a greater vulnerability to later immune insults and subsequent depressive/anxiety symptoms.<sup>65</sup>

#### FINAL REMARKS

From the ever-expanding literature connecting immune dysregulation with both mood and anxiety disorders, it is possible to deduce an obvious bearing of inflammation on these neuropsychiatric illnesses. However, literature reporting an association with anxiety disorders is at present relatively sparse and demands further investigation. Progression of understanding is also impeded by inconsistencies among results reporting cytokine levels and a need to formulate a homogeneous approach to protocols, including the consideration of confounding variables. Nonetheless, recent advances describing inflammatory mechanisms affecting behavior, such as impacts on neurotransmitter and neuroendocrine function and on synaptic plasticity, provide promising indications although complete understanding has yet to be achieved and it is difficult to confirm causality due to the bidirectional nature of the association. Nevertheless, the current understanding suggests that at least subgroups of individuals with mood or

anxiety disorder have elevated levels of inflammation, which is a critical mediator in the pathogenesis of the disorders. In relation to clinical relevance, in an age where the potential consequences of inflammation on our physical health are increasingly well understood, the risk to patients too should be acknowledged, and interventions planned accordingly. Indeed, possible future directions of research will be to work toward better stratification and personalization of treatments, using diagnostic and biomarker measures to identify individuals that might benefit most from treatment targeting inflammation for the sake of their physical and mental health.

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