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Elevated immune-inflammatory signaling in mood disorders: a new therapeutic target?

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Abstract

Converging translational evidence has implicated elevated immune-inflammatory signaling activity in the pathoetiology of mood disorders, including major depressive disorder and bipolar disorder. This is supported in part by cross-sectional evidence for increased levels of proinflammatory eicosanoids, cytokines and acute-phase proteins during mood episodes, and prospective longitudinal evidence for the emergence of mood symptoms in response to chronic immune-inflammatory activation. In addition, mood-stabilizer and atypical antipsychotic medications downregulate initial components of the immune-inflammatory signaling pathway, and adjunctive treatment with anti-inflammatory agents augment the therapeutic efficacy of antidepressant, mood stabilizer and atypical antipsychotic medications. Potential pathogenic mechanisms linked with elevated immune-inflammatory signaling include perturbations in central serotonin neurotransmission and progressive white matter pathology. Both heritable genetic factors and environmental factors including dietary fatty-acid composition may act in concert to sustain elevated immune-inflammatory signaling. Collectively, these data suggest that elevated immune-inflammatory signaling is a mechanism that is relevant to the pathoetiology of mood disorders, and may therefore represent a new therapeutic target for the development of more effective treatments.

Keywords

arachidonic acid; bipolar disorder; C-reactive protein; coronary heart disease; cytokines; immunology; inflammation; major depressive disorder; omega-3 fatty acids; prostaglandins; serotonin

Major mood disorders including major depressive disorder (MDD) and bipolar disorder (BD) represent a major public health problem. In the year 2000, the WHO identified MDD

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as the fourth ranked cause of disability and premature death in the world, and projected that by 2020 MDD will be the second most important cause of disability worldwide after cardiovascular disease [1,2]. In the USA, the lifetime prevalence rates for MDD are 2–7%, and up to 16–20% suffer from milder forms of the illness, and the life-time prevalence rates for BD are estimated at 1.0% for bipolar I disorder (BD-I), 1.1% for BD-II and 2.4% for subthreshold BD (4.4% total) [3]. The initial onset of mania and MDD most frequently occurs during childhood and adolescence [4–6], and MDD frequently precedes the initial onset of mania [7]. Outcomes data indicate that MDD and BD are chronic relapsing and remitting illnesses associated with significant psychosocial morbidity [8,9] and excess premature mortality attributable primarily to suicide and cardiovascular-related disorders [10,11]. There is therefore an urgent need to develop a better understanding of risk and resilience factors associated with the development and progression of MDD and BD to inform improvements in treatment and ultimately prevention strategies.

Major advances in the treatment and prevention of mood disorders will be galvanized by the identification of pathogenic mechanisms conferring vulnerability to pathophysiological features (i.e., endophenotypes) associated with mood dysregulation. Aggressive efforts have been devoted to identify associations between susceptibility genes and clinical diagnostic criteria, although a consistent pattern has yet to emerge owing in part to the polygenic, heterogeneous and multifactorial nature of these disorders. Indeed, subtotal heritability estimates for MDD [12–14] and BD [15–17], and large cross-national variations in the life-time prevalence rates of MDD and BD [18], suggest that both genetic and environmental factors confer risk for developing these disorders. Accordingly, there is a need to develop a better understanding of the link among gene–environment interactions, intermediate endophenotypes and mood dysregulation.

There is a growing body of evidence that suggests that elevated immune-inflammatory signaling may represent a pathogenic mechanism that contributes to mood and metabolic dysregulation in MDD and BD. The primary objective of this article is to review translational evidence implicating immune-inflammatory signaling in the pathophysiology of mood disorders, and to review the effects of medications used to treat mood symptoms on immune-inflammatory signaling. In addition, the authors explore potential mechanisms by which elevated proinflammatory signaling cascades may contribute to prominent pathophysiological features associated with mood disorders, as well as candidate genetic and environmental factors that may contribute to immune-inflammatory dysregulation in an effort to identify candidate therapeutic targets.

Immune-inflammatory status

Immune-inflammatory signaling is mediated, in part, by circulating peripheral blood mononuclear cells (PBMCs), including lymphocytes, leukocytes, neutrophils as well as central microglia and astrocytes, and involves an array of interacting signaling molecules. In brief, the long-chain omega-6 fatty acid arachidonic acid, derived from dietary linoleic acid via a series of desaturation and elongase reactions, becomes acetylated into the *sn*-2 position of membrane phospholipids. Phospholipid-bound arachidonic acid is mobilized via a calcium-dependent cytosolic isoform of phospholipase A_2 ($cPLA_2$), and free arachidonic acid is a substrate for cyclooxygenase (COX)-mediated biosynthesis of prostaglandins (i.e., PGH_2), thromboxanes and prostacyclins, as well as lipoxygenase-mediated biosynthesis of leukotrienes. COX-generated PGH_2 is converted to PGE_2 via PGE synthase, and PGE_2 stimulates the biosynthesis of downstream proinflammatory cytokines including IL-6 at the level of transcription [19–21]. Proinflammatory cytokines including IL-6, IL-1β and TNF-α in turn stimulate hepatic biosynthesis of acute-phase proteins including C-reactive protein (CRP [22–24]). In contrast to arachidonic acid, the long-chain omega-3 (LC*n*-3) fatty acids,

including eicosapentaenoic acid (EPA; 20:5*n*-3) and docosahexaenoic acid (DHA; 22:6*n*-3), are predominantly anti-inflammatory and EPA competes with arachidonic acid for metabolism by COX enzymes [25]. In addition, COX and lipoxygenase metabolites of DHA and EPA (i.e., D- and E-series resolvins) have potent inflammation-resolving properties (Figure 1) [26–29].

Several case–control studies have investigated the immune-inflammatory status of MDD patients. An early series of studies observed elevated PGE_2 levels in the saliva, plasma or CSF of MDD patients [30–34], and that PGE_2 levels were positively associated with depression symptom severity [32,33]. Because reductions in LC*n*-3 fatty acids, and associated elevations in the arachidonic acid/LC*n*-3 ratio, are associated with elevations in PLA_2 and COX-2 expression and activity [35], it is relevant that a meta-analysis of 14 case–control fatty acid composition studies found that MDD patients exhibit significant reductions in LC*n*-3 fatty acids, and elevations in the arachidonic acid/LC*n*-3 ratio, in erythrocytes and plasma [36]. Some studies [37–39], but not all [40], found that the arachidonic acid/EPA ratio was positively correlated with depression symptom severity. Several case–control studies have investigated circulating cytokine levels in MDD patients, and a recent meta-analysis of 24 studies found significantly higher blood concentrations of IL-6 and TNF-α, and that there were no significant differences for other proinflammatory (IL-1β, IL-2, IFN-γ) or anti-inflammatory (IL-4, IL-8, IL-10) cytokines [41]. Case–control studies have also observed higher levels of the acute-phase protein CRP in MDD patients [41–46], and that higher CRP levels are associated with an increased adjusted risk for past and current depressive episodes [47–49]. Together, these data suggest that MDD is associated with abnormal elevations in immune-inflammatory signaling analogous to a sustained low-grade systemic inflammatory condition.

Several case–control studies have investigated the immune-inflammatory status of patients diagnosed with BD [50]. A preliminary cross-sectional study found that serum PLA_2 activity was elevated in BD patients [51]. Consistent with elevated PLA_2-mediated arachidonic acid mobilization and loss from phospholipids, one study found that erythrocyte phospholipid arachidonic acid levels were significantly lower in acutely manic patients [52]. Another study found that the arachidonic acid/EPA ratio was positively correlated with manic symptom severity in a small group (n = 10) of acutely manic patients, and did not observe any changes in PGE_2 levels [53]. The majority of case–control studies have found that BD patients exhibit greater IL-6, IL-6R, IL-2R, IL-1β and/or TNF-α levels during depressive and acute manic episodes compared with healthy controls [54–62]. Cross-sectional studies have also observed greater CRP levels in BD patients during acute mania and/or a depressive phase compared with healthy controls [63–66]. Some studies [54,67–69], but not all [57,63], have found that IL-6 or CRP levels are positively correlated with manic or depression symptom severity. Euthymic BD patients exhibit no differences or reductions in TNF-α, IL-6 and/or CRP compared with healthy controls [54,63,70], which may be attributable in part to medication effects (see the below paragraphs). Interestingly, asymptomatic offspring of BD parents, who are at increased risk for developing a mood disorder [8], exhibit a PBMC gene expression signature indicative of elevated immune-inflammatory signaling [60]. Acutely manic patients also exhibit elevated immunoglobulin and compliment protein levels [65], and BD is associated with increased prevalence of autoimmunity to pathogenically relevant antigens, including glutamic acid decarboxylase-65 [71] and thyroperoxidase [72]. These data suggest that elevated immune-inflammatory signaling is observed during both manic and depressive phases of BD, resolves during euthymia in response to pharmacotherapy and may precede the initial onset of mood symptoms in BD offspring.

A smaller number of case–control studies have investigated cytokine levels in the CSF of MDD and BD patients, and the results have been inconsistent. One study found that medication-free patients with acute-severe depression had higher CSF concentrations of IL-1β, lower IL-6 and no change in TNF-α [73]. A second study observed lower CSF concentrations of IL-6 and IL-6R in medicated geriatric MDD patients [74]. A third study did not observe altered CSF IL-6 concentrations in medication-free MDD patients [75]. A fourth study found that medicated euthymic BD patients exhibited greater CSF IL-1β levels, and lower CSF IL-6 levels, compared with a healthy control [76].

Case–control studies have also investigated the expression of inflammatory signaling markers in postmortem brain tissue from MDD and/or BD patients. One study found that $cPLA_2$, membrane PGE synthase and COX-2 were elevated, and COX-1 and cytosolic PGE synthase reduced, in the postmortem frontal cortex of predominantly medicated BD patients [77]. A second study did not find changes in COX-1 or COX-2 expression in postmortem frontal cortex of predominantly medicated patients with MDD or BD, and observed significant reductions in cytosolic PGE synthase, which was attributable to medication effects in BD [78]. A third study did not observe any differences in $cPLA_2$ or calcium-independent phospholipase A_2 ($iPLA_2$) in postmortem brains of predominantly lithium-treated BD patients, but did find that $iPLA_2$ activity was significantly greater in BD patients with a history of psychosis [79]. Consistent with elevated $cPLA_2$ activity, arachidonic acid composition was lower in the postmortem frontal cortex of unmedicated BD patients, and was partially normalized in patients treated with mood-stabilizer medications prior to death [80]. Another fatty acid composition study did not observe significant alterations in postmortem cortex arachidonic acid composition in predominantly medicated BD patients [81]. Regarding postmortem brain cytokine levels, one study found that transmembrane TNF protein expression was significantly greater in the frontal cortex of predominantly medicated MDD patients compared with controls [82], and a second study observed higher protein and mRNA levels of IL-1β and IL-1R, but not TNF-α, in the frontal cortex of predominantly medicated BD patients [83].

In view of the high prevalence rate of suicide in MDD and BD, it is relevant that CSF IL-6 concentrations were significantly elevated in those who attempted suicide compared with healthy controls, and there was a significant positive correlation between CSF IL-6 levels and depression symptom severity [84]. A postmortem brain study observed a trend for greater TNF-α expression in the frontal cortex of female suicide victims, no changes in IL-1β, IL-5 or IL-6 expression, greater IL-4 mRNA expression in female suicide victims, and greater IL-13 mRNA expression in male suicide victims [85]. A second postmortem brain study found that IL-6, IL-1β, and TNF-α mRNA and protein levels were significantly higher in the frontal cortex of male and female adolescent suicide victims [86]. Postmortem brain fatty acid composition studies have not observed significant alterations in arachidonic acid composition in adult suicide victims [87], and that the arachidonic acid/DHA ratio was inversely correlated with age at death in adolescent controls but not in suicides [88]. Erythrocyte or plasma LC*n*-3 composition was found to be significantly reduced in suicidal patients [89,90], and a prospective study found that low baseline plasma DHA composition was a significant predictor of future suicide attempts in medication-free MDD patients [91].

Additional evidence implicating inflammation in the pathoetiology of mood dysregulation comes from prospective studies of human subjects chronically administered the proinflammatory cytokine IFN-α for the treatment of infectious diseases including hepatitis C. Approximately 30% of subjects receiving chronic IFN-α therapy develop clinically significant depression, which typically responds to conventional antidepressant medications [92–94], and approximately 25% of patients exhibit hypomanic and manic features, including irritability, sleep disturbances, labile anger and hyperactivity [95–98]. Depressive

symptoms resulting from IFN-α treatment are associated with greater treatment-emergent increases in plasma IL-6 concentrations [99]. Moreover, IFN-α treatment is associated with elevations in CSF IL-6 concentrations, which are inversely correlated with CSF levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIA A), and CSF 5-HIAA concentrations were a significant predictor of depressive symptoms [100]. A subset of healthy subjects treated with the endotoxin *Salmonella abortusequi* also exhibit symptoms of depression and anxiety, which were correlated with increases in plasma IL-6 and TNF-α [101]. Another study found that elevations in IL-6 levels in response to influenza vaccination were amplified and prolonged in elderly patients with depressive symptoms [102]. This body of evidence suggests that repeated activation of immune-inflammatory signaling networks can precipitate depression and/or manic-like symptoms in a subset of human patients.

Consistent with these clinical observations, a body of preclinical evidence suggests that elevated immune-inflammatory cytokine production increases behavioral indices of sickness and depression in rodents [103], whereas TNF-α receptor [104] and IL-6 [105] knockout mice exhibit reduced behavioral indices of depression. In rhesus monkeys, 4-week IFN-α administration led to elevations in plasma IL-6 concentrations and a persistent increase in anxiety- and depressive-like behavior in a subset of animals [106]. Consistent with a sensitization mechanism, repeated exposure to TNF-α is associated with an enduring enhancement of behavioral, neurochemical and neuroendocrine responses to a second TNF-α injection [107]. Dietary-induced reductions in *n*-3 fatty acids, and associated elevations in the arachidonic acid/DHA ratio, are associated with elevated PLA_2 and COX-2 expression and activity in rat brain [35], elevated constitutive IL-6, TNF-α and CRP concentrations in rat plasma [108], greater lipopolysaccharide (LPS)-stimulated elevations in IL-6 in rodent plasma [109], and elevated behavioral indices of depression and aggression [110]. The olfactory bulbectomized rat model of depression is associated with elevated central PLA_2 activity and proinflammatory PGE_2 production [111,112], and the Flinders Sensitive Line rat model of depression is associated with greater regional brain arachidonic acid levels, and associated elevations in the arachidonic acid/DHA ratio [113]. These preclinical studies support a positive association between elevated immune-inflammatory signaling and depressive-like behavioral symptoms in animals, and suggest mediation by both environmental (i.e., dietary *n*-3 fatty acid intake) and genetic (i.e., inbred rat strains) factors.

Although beyond the scope of this review, elevated immune-inflammatory signaling has long been recognized to play a pivotal role in the etiology and progression of cardiovascular- and circulatory-related disorders [114], and MDD and BD are both associated with excess premature mortality attributable in part to these disorders [10,11]. Elevated CRP levels are an independent predictor of cardiovascular events and mortality [115], and use of low-dose aspirin, a COX-1 inhibitor, is associated with significant risk reduction among men with elevated CRP levels [116]. Elevated IL-6 levels may also be associated with elevated risk for developing coronary artery disease [117–119], and multiple lines of evidence suggest that the low LC*n*-3 fatty acid status exhibited by MDD and BD patients places them at increased risk for sudden cardiac death [120,121]. Furthermore, BD patients exhibit a high prevalence of obesity and metabolic syndrome [122–126], both of which are associated with elevated immune-inflammatory signaling [127,128]. Life-time and current prevalence rates of asthma, a chronic inflammatory disorder, are elevated in patients with mood disorders, particularly BD [129]. These data suggest that elevated immune-inflammatory signaling may be associated with prominent medical comorbidities frequently observed in MDD and BD patients.

Medication effects

Selective serotonin reuptake inhibitors (SSRIs) are currently a first-line treatment for mood symptoms in children, adolescents and adults with MDD, although a subset of patients fail to achieve symptomatic remission following chronic SSRI treatment [130]. Although controversial, SSRI medications may also increase risk of self-injury and suicidal ideation in a subset of pediatric and adolescent MDD patients [131]. Moreover, an emerging body of evidence suggests that treatment with antidepressants, particularly those with noradrenergic augmenting effects, may precipitate and possibly accelerate the onset of mania and suicidal ideation in susceptible children and adolescents [132–135]. Double-blind placebo-controlled clinical trials have found that mood-stabilizer medications that exhibit efficacy in adult BD patients, including lithium and valproic acid, have limited efficacy in the treatment of depressive mood symptoms in youth at very high risk for developing mania [136,137]. Chronic valproic acid treatment is also associated with weigh gain and insulin resistance in youth [138]. Atypical antipsychotic medications, including olanzapine, risperidone and quetiapine, are efficacious for the treatment and management of manic symptoms [139–141], and are used as adjunctive therapy in treatment-resistant depression, but are associated with clinically significant metabolic side-effects including excess weight gain and insulin resistance [142,143]. These findings highlight the urgent need to develop evidence-based treatments for mood disorders with improved efficacy, safety and tolerability.

Although some evidence suggests that antidepressant medications interact with immune-inflammatory signaling pathways, the results have been inconsistent and the mechanisms remain poorly understood [144]. Basic science studies have found that different antidepressant medications suppress LPS-induced production of proinflammatory cytokines including TNF-α and IL-6 [145], and reduce the development of cytokine-induced depressive-like behavior in rodents [146]. An *in vitro* study found that tricyclic and SSRI antidepressants blunted cytokine-induced PGE_2 production in human synovial cells [147]. However, rodent studies have also found that the tricyclic desipramine, a noradrenergic reuptake inhibitor, increases IL-1β mRNA levels in the rat hypothalamus [148], and chronic treatment with different classes of antidepressants upregulate PLA_2-mediated arachidonic acid turnover in rat brain [149,150]. Because the effects of antidepressants on PLA_2-mediated arachidonic acid turnover are opposite to those of mood-stabilizer medications [151], this mechanism may contribute to antidepressant-induced manic switching observed in BD patients [150,152].

Clinical studies have found that subchronic treatment with SSRI medications do not significantly alter serum IL-6 or IL-1β concentrations in MDD patients [153,154], and that greater IL-6 and CRP levels may be associated with antidepressant treatment resistance [155,156]. Another study found that greater pretreatment CRP levels in MDD patients were significantly reduced following 6-week antidepressant treatment in both responders and nonresponders [45]. Adjunctive treatment with celecoxib, a selective COX-2 inhibitor, was found to augment the therapeutic efficacy of the noradrenergic reuptake inhibitor reboxetine in MDD patients [157,158]. A 6-week controlled trial found that adjunctive treatment with celecoxib also augmented the therapeutic efficacy of fluoxetine in MDD patients [159]. Adjunctive treatment with acetylsalicylic acid (aspirin), a COX-1 inhibitor, increased remission rates when added to fluoxetine in MDD patients previously nonresponsive to fluoxetine alone [160]. Adjunctive LC*n*-3 fatty acids augmented the therapeutic efficacy of fluoxetine [161] and citalopram [162] in MDD patients, and reduced symptom severity in MDD patients that were refractory to standard antidepressant treatment [163]. These preliminary clinical findings suggest that adjunctive treatment with anti-inflammatory agents augment the therapeutic efficacy of anti-depressant medications, and suggest that antidepressants may act on downstream neurochemical consequences of elevated immune-

inflammatory signaling (i.e., decreasing serotonin turnover) rather than direct effects on signaling activity.

A common mechanism of action of mood-stabilizer medications, including lithium chloride and the anticonvulsants valproic acid and carbamazepine, is the downregulation of $cPLA_2$-mediated arachidonic acid mobilization from phospholipids and associated reductions in COX-2-mediated PGE_2 production in rat brain [151]. Consistent with reductions in $cPLA_2$-mediated arachidonic acid mobilization and loss, chronic lithium treatment is associated with elevated arachidonic acid composition in rodent erythrocytes and regional brain [164]. This body of preclinical evidence supports the 'arachidonic acid cascade' hypothesis, which posits that the therapeutic actions of mood-stabilizer medications are mediated in part by COX-2 substrate (arachidonic acid) sequestration in phospholipids and associated reductions in PGE_2 production [165]. A recent study found that neuroinflammation elicited by chronic intracerebroventricular administration of the endotoxin LPS was associated with elevated central $cPLA_2$ activity and PGE_2 production, and this response was significantly blunted in rats chronically treated with lithium [166]. The implication of these findings is that elevations in arachidonic acid→PGE_2 biosynthesis leading to neuroinflammation are a pathogenic mechanism underlying the development BD [167].

In general agreement with these preclinical findings, emerging clinical evidence suggests that mood-stabilizer medications downregulate proinflammatory signaling pathways in BD patients. An *ex vivo* study found that LPS-stimulated PBMC IL-6 production was greater in medication-free BD patients compared with healthy controls, and that this response was attenuated in lithium-treated patients [168]. A second study found that lithium-treated BD patients exhibited fewer IL-6-secreting PBMCs compared with healthy controls, and that the number of IL-6-secreting cells decreased significantly in medication-naive BD patients following chronic lithium treatment [70]. In rapid cycling BD patients, serum IL-2R and IL-6R were increased compared with healthy controls, and decreased significantly following 4-week lithium treatment [169]. Another study found that 6-week lithium and/or valproate treatment significantly reduced elevated IL-6R and IL-6, but not TNF-α, levels in BD patients [56], whereas another study did not observe significant alterations in elevated IL-6R and IL-2R in manic patients following 2-week valproate treatment [55]. Preliminary evidence further suggests that adjunctive treatment with anti-inflammatory agents, including celecoxib [170], aspirin [171] and LC*n*-3 fatty acids [172,173], augment the therapeutic efficacy of mood-stabilizer medications.

Zyprexa, Cloazapine

Atypical antipsychotic medications are high-affinity antagonists at serotonin $5\text{-}HT_{2A/C}$ and dopamine D_2 receptors [174], both of which are positively coupled to $cPLA_2$ [175–180]. Chronic treatment with olanzapine or clozapine decreased $cPLA_2$-mediated arachidonic acid turnover in cortical phospholipids, and decrease COX-2 activity and PGE_2 concentrations, in rat brain [181,182]. Preclinical studies have also found that atypical antipsychotic medications significantly attenuate greater IL-6 and TNF-α production in microglia cells following IFN-γ exposure [183,184], and in mice following peripheral LPS administration [185]. Chronic risperidone normalized constitutively elevated plasma IL-6, TNF-α and CRP levels in LC*n*-3 fatty acid-deficient rats [186]. Clinical studies suggest that antipsychotic medications may have immunosuppressive properties in schizophrenic patients, although the results have been inconsistent [187]. Adjunctive treatment with the COX-2 inhibitor celecoxib was superior to risperidone alone for reducing symptom severity in schizophrenic patients [188]. Adjunctive LC*n*-3 fatty acid (EPA) supplementation was also found to accelerate treatment response, improve tolerability and permitted a 20% reduction in atypical antipsychotic dose in first-episode psychotic patients [189]. Together, these data suggest that atypical antipsychotic medications, such as mood stabilizers, suppress immune-inflammatory signaling activity.

Pathogenic mechanisms

Central serotonin (5-HT) neurotransmission has repeatedly been implicated in the pathophysiology [190] and treatment [191] of MDD. Medication-free MDD patients exhibit reduced indices of serotonin synthesis [192], and significantly greater internal, jugular veno-arterial plasma content of 5-HIAA relative to healthy controls [193]. In contrast, chronic treatment with the SSRI fluoxetine significantly decreases the 5-HIAA content in CSF of MDD patients [193–197] and serotonin turnover (i.e, 5-HIAA/5-HT ratio) in rat frontal cortex [198,199]. Preclinical studies have found that peripheral administration of IL-6 significantly increases extra-cellular serotonin concentrations and serotonin turnover in rat brain [200,201]. Moreover, central 5-HIAA levels were elevated following peripheral administration of IL-1β or TNF-α [202], and chronic peripheral administration of IFN-α increased serotonin turnover in rat frontal cortex [203]. Prior LPS exposure resulted in greater increases in amygdala 5-HIAA levels in response to a second TNF-α injection [204]. Furthermore, chronic dietary LC*n*-3 fatty acid deficiency is associated with constitutive elevations in plasma IL-6, which are positively correlated with serotonin turnover in rat brain [108]. These and other data suggest that elevated peripheral cytokine production may be sufficient to alter central serotonin metabolism in a direction that is opposite to that produced by SSRI medications.

Several independent findings have implicated hypothalamic–pituitary–adrenal (HPA) axis dysregulation in the pathophysiology of mood disorders [205,206], and emerging preclinical evidence suggests that proinflammatory cytokines alter HPA axis activity and reactivity. Specifically, acute cytokine stimulation by LPS induces the expression and release of corticotropin-releasing hormone, adrenocorticotropic hormone and corticosterone in rats [200,207,208]. Acute and chronic stress is associated with elevations in central and/or peripheral proinflammatory cytokine levels including IL-1β and IL-6 [148,209]. Consistent with a cross-sensitization of HPA-axis reactivity and immune-inflammatory signaling, prior exposure to stressors sensitize the neuroinflammatory response to peripheral and central immune challenge [210], and prior LPS exposure is associated with greater HPA axis reactivity (i.e., plasma corticosterone levels) in response to second TNF-α injection [204]. Cytokines have also been found to decrease glucocorticoid receptor expression and nuclear translocation, leading to the desensitization of glucocorticoid receptor-mediated negative feedback on the HPA axis [211]. It is also of interest that LC*n*-3 fatty acid supplementation significantly blunted LPS-induced elevations in plasma cortisol and adrenocorticotropic hormone levels in human subjects [212,213]. These preliminary findings support a link between elevated immune-inflammatory signaling and HPA axis dysregulation observed in patients with mood disorders.

Elevated immune-inflammatory signaling associated with T-lymphocyte activation and central infiltration has long been recognized as a mechanism central to the etiology of white matter pathology in multiple sclerosis [214]. Similar to BD and MDD, multiple sclerosis is a progressive disorder with a relapsing-remitting course, and mood disorders are highly prevalent among multiple sclerosis patients [215–217]. Furthermore, levels of IL-2 and IL-2R (CD25), markers of T-lymphocyte activation, are elevated in serum and CSF of relapsing multiple sclerosis patients [218,219] and in serum of manic patients [55,59,61,220]. As observed in multiple sclerosis patients [214], myelin-associated gene expression [221,222] and myelin staining [223] are reduced in postmortem brain of BD and MDD patients, and diffusion tensor imaging studies have revealed deficits in central white matter structural integrity (i.e., reduced fractional anisotropy) in patients with multiple sclerosis [224], BD [225–227] and MDD [228,229]. Consistent with these clinical observations, animal studies have demonstrated that elevated immune-inflammatory signaling leads to demyelination [230–233], and that increasing dietary LC*n*-3 fatty acid

intake is protective against white matter injury [234,235]. Together, these associations suggest that there may be a previously unrecognized link between elevations in immune-inflammatory signaling and progressive white matter pathology observed in patients with mood disorders.

Meta-analyses of cross-sectional structural imaging studies have also identified lateral ventricular enlargement and reductions in hippocampal volume, as robust and consistent features associated with mood disorders [236,237]. It is relevant, therefore, that *in vivo* imaging and *ex vivo* studies have found that neuroinflammation elicited by chronic central LPS administration is associated with lateral ventricular enlargement and decreased hippocampal size in rats [238,239]. Furthermore, neuroinflammation is associated with elevated COX-2-mediated PGE_2 production in rat brain [166], and PGE_2-mediated signaling has neurotoxic and synaptotoxic effects [240–242]. Moreover, proinflammatory cytokines can lead to the generation of tryptophan-kynurenine metabolites including glutamate agonists, which have excitotoxic effects [243]. It is also relevant that greater habitual dietary LC*n*-3 fatty acid intake is associated with larger cortical gray matter volumes in several corticolimbic regions found to exhibit volume reductions in MDD and/or BD patients, including the hippocampus, amygdala and anterior cingulate cortex [244].

Etiological mechanisms

Although the etiologic mechanisms contributing to dysregulated immune-inflammatory homeostasis in mood disorders are poorly understood, existing evidence suggests that environmental factors may play a significant role. For example, based on concordance rates of elevated markers of immune-inflammatory signaling in circulating PBMCs among BD twins, it was concluded that elevated signaling activity was primarily attributable to shared environmental factors rather than genetic factors [245]. Candidate environmental factors that may contribute to elevated immune-inflammatory signaling activity in mood disorders include increased sensitivity or exposure to infectious agents [246], increased sensitivity to seasonal allergies [247,248] and increased sensitivity to commonly consumed food components (i.e., gluten [249]). In addition, stressful life events and psychosocial stressors have long been recognized as distal and proximal antecedents of mood dysregulation [250], and childhood maltreatment or psychosocial stress are associated with greater IL-6 and/or CRP production in adulthood [251–253]. Like MDD and BD, post-traumatic stress disorder is also associated with sustained elevations in immune-inflammatory signaling activity [254,255]. Moreover, elevations in IL-6 in response to psychosocial stress were found to be greater in MDD patients with a history of early-life stress [256]. Therefore, these environmental factors may lead to a sensitization of immune-inflammatory signaling in patients with mood disorders.

In view of the principal role of the omega-6 fatty acid arachidonic acid in the initiation of immune-inflammatory signaling, another potentially relevant environmental factor is habitual dietary arachidonic acid intake. Over the latter half of the 20th Century, foods/oils that contain higher levels of arachidonic acid, including peanut, soybean, canola oils and red meat, poultry, pork, have increased substantially in the US diet [257]. Controlled feeding studies have found that increasing dietary arachidonic acid intake is associated with elevated *ex vivo* PBMC production of PGE_2, but not IL-1β, IL-2, IL-6 or TNF-α, in healthy human subjects [258], and elevated production of PGE_2 in rat blood and brain [259,260]. Increasing dietary arachidonic acid intake was also associated with greater PBMC proliferation in response to influenza vaccine in healthy human subjects [261]. Although these data suggest that dietary arachidonic acid may contribute in part to elevated PGE_2 levels observed in mood disorders, it does not appear sufficient at the doses investigated to account for elevated levels of proinflammatory cytokines observed in patients with mood disorders. Nevertheless,

additional research is needed to determine whether the dietary intake of arachidonic acid is greater in mood disorder patients.

In contrast to omega-6 fatty acids, greater dietary intake of LC*n*-3 fatty acids, found predominantly in fatty cold-water fish including salmon, trout and tuna [262], is associated with reduced markers of immune-inflammatory signaling, including IL-6, TNF-α and CRP in healthy human subjects [263–271]. For example, in a cohort of 1123 human subjects, lower fasting plasma LC*n*-3 fatty acid composition was associated with significantly higher IL-6 and TNF-α concentrations [267]. Other studies have found that greater habitual dietary LC*n*-3 fatty acid intake is inversely correlated with plasma IL-6 and CRP levels [266,268], and that dietary supplementation with LC*n*-3 fatty acids (fish oil) decrease PBMC production of TNF-α in healthy subjects [263–265]. Case–control studies have found that peripheral indices of dietary LC*n*-3 fatty acid intake are significantly lower in patients with MDD [36] and BD [40,52,272], and cross-national and cross-sectional epidemiological studies suggest that greater habitual dietary LC*n*-3 fatty acid intake is associated with reduced life-time prevalence rates of MDD and BD [273–276]. Independent meta-analyses of controlled intervention trials have found that chronic dietary LC*n*-3 fatty acid (EPA + DHA) supplementation is associated with significant reductions in depression symptom severity in MDD and BD patients [277–279]. These data suggest that lower dietary LC*n*-3 fatty acid intake, and associated elevations in the arachidonic acid/LC*n*-3 fatty acid ratio, represent a modifiable risk for elevated immune-inflammatory signaling in mood disorders.

A number of candidate genetic factors may also elevate immune-inflammatory signaling in mood disorders. The first and rate limiting step in the biosynthesis of arachidonic acid from its dietary precursor linoleic acid is Δ6-desaturase activity (*FADS2*), and preclinical studies have found that *FADS2* deletion [280] or selective pharmacological inhibition of Δ6-desaturase activity [281] significantly blunts eicosanoid production. Converging evidence from human genotyping studies further suggest that *FADS2* gene variants are strongly correlated with arachidonic acid levels in plasma, erythrocytes and breast milk [282], and *FADS2* haplotypes and/or Δ6-desaturase activity estimates are correlated with proinflammatory markers including CRP [283,284]. *FADS2* haplotypes and/or Δ6-desaturase activity estimates have also been linked with disorders associated with immune-inflammatory dysregulation, including allergies [285,286] and cardiovascular disease [284,287]. The *FASD2* gene is colocalized to chromosome 11q12–11q13.1 [288], a locus found in genome-wide association studies to be associated with arachidonic acid status [289], inflammatory/immune disorders [290–293], cardiovascular disorders [294] and BD [295]. Elevated *FADS2* expression and activity indices have also been observed in BD patients [40,296]. This body of evidence suggests that augmentation of linoleic acid→arachidonic acid→PGE_2 biosynthesis secondary to *FADS2* gene variants represents a candidate risk mechanism for elevated immune-inflammatory signaling in mood disorders.

The mobilization of arachidonic acid from phospholipids is mediated by calcium-dependent cytosolic $cPLA_2$, and the PLA_2BanI polymorphism is associated with greater platelet PLA_2 enzyme activity in schizophrenic patients [297]. Genetic association studies have found that the PLA_2 BanI polymorphism may be associated with MDD, but not BD [298–300], and a recent prospective study found that the PLA_2 BanI polymorphism was associated with more somatic symptoms of depression following IFN-α treatment [301]. Genetic studies have also identified a putative association between polymorphisms in IL-1β [302] and the TNF-α promoter [303–305] in BD. The TNF-α polymorphism is also associated with more labile anger in subjects receiving chronic IFN-α therapy [97]. Moreover, a COX-2 polymorphism was associated with increase the risk of developing depression in response to IFN-α treatment [301]. The inter-relationship between these preliminary candidate genetic factors,

immune-inflammatory status in mood disorders, and environmental factors warrant additional investigation.

Conclusion

Converging translational evidence suggests that mood disorders are associated with elevated immune-inflammatory signaling activity. Mood-stabilizer and atypical antipsychotic medications downregulate common initial components of the immune-inflammatory signaling pathway, and adjunctive treatment with anti-inflammatory agents augment the therapeutic efficacy of antidepressant, mood-stabilizer and atypical antipsychotic medications. Elevated immune-inflammatory signaling activity may contribute to pathogenic processes leading to perturbations in central serotonin neurotransmission and HPA-axis reactivity, as well as progressive white and gray matter pathology. Both genetic factors, including polymorphisms in key immune-inflammatory molecules, and modifiable environmental factors, including dietary LC*n*-3 fatty acid insufficiency, may contribute to elevated immune-inflammatory signaling. Collectively, these data suggest that elevated immune-inflammatory signaling is relevant to the pathoetiology of mood disorders, and represents a therapeutic target for the development of improved therapeutic strategies. It is proposed that early negative modulation of immune-inflammatory signaling may increase resilience to progressive neuropathological changes in youth at risk for developing mood disorders, and that safe and well-tolerated anti-inflammatory agents including LC*n*-3 fatty acids may represent an efficacious and safe early intervention option. Future research in this field holds tremendous promise for developing a new appreciation for the role of immune-inflammatory signaling in the pathoetiology of mood disorders, and may ultimately lead to novel preventative strategies as well as a treatment paradigm shift in psychiatric practice.

Expert commentary

A converging body of evidence suggests that elevated immune-inflammatory signaling may represent a feature that is relevant to the pathophysiology of mood disorders. Specifically, cross-sectional studies have found that patients with mood disorders exhibit elevated peripheral levels of immune-inflammatory signaling markers compared with healthy controls. The most robust and consistent findings have been for the proinflammatory cytokines IL-2, IL-6, IL-1β and TNF-α, and the acute-phase protein CRP. Cross-sectional evidence for similar changes in CSF and postmortem brain tissue has been less consistent, potentially due to medication effects. Indeed, mood-stabilizer and atypical anti-psychotic medications suppress initial components of the immune-inflammatory signaling pathway, and adjunctive treatment with anti-inflammatory agents, including selective COX-2 inhibitors and LC*n*-3 fatty acids, augment the therapeutic efficacy of anti-depressant, mood-stabilizer and atypical antipsychotic medications. Prospective longitudinal studies have found that chronic induction of immune-inflammatory activity is associated with the emergence of both depressive and manic-like mood symptoms in human subjects. Last, preclinical studies employing different animal models have demonstrated that experimental induction of peripheral and central immune-inflammatory signaling is associated with behavioral indices of depression, as well as neurochemical and neuroanatomical alterations that recapitulate clinical findings. Collectively, this body of evidence implicates elevated immune-inflammatory signaling as a pathogenic mechanism in mood disorders.

It is not currently clear if immune-inflammatory signaling represents a state or trait feature of mood disorders. Several observations suggest that elevated immune-inflammatory signaling may be a state feature: indices of elevated immune-inflammatory signaling observed in acutely manic or depressed patients are attenuated in euthymic patients, immune-inflammatory markers have been found to be positively correlated with mood

symptom severity and the induction of immune-inflammatory signaling is frequently associated with the emergence of both depressive and manic-like mood symptoms in human subjects that do not have a personal or family history of mood disorders. However, several observations also suggest that elevated immune-inflammatory signaling may be a trait feature: asymptomatic offspring of BD parents exhibit elevated immune-inflammatory signaling, polymorphisms in genes that regulate immune-inflammatory signaling have been identified as potential susceptibility alleles and the immunosuppressive effects of medications may account for why euthymic patients do not show elevated immune-inflammatory signaling.

It is also not currently clear what etiological factors contribute to elevated immune-inflammatory signaling in patients with mood disorders, and both environmental and genetic factors may act in concert to trigger, sensitize and sustain elevated immune-inflammatory signaling (Figure 2). Central to the question of whether elevated immune-inflammatory signaling is relevant to the pathoetiology of mood disorders is the identification of plausible mechanisms linking immune-inflammatory signaling and mood dysregulation. Different lines of evidence suggest that two mediating mechanisms are alterations in central serotonin metabolism and HPA-axis dysregulation. In addition, the pathogenic mechanism may be progressive in nature and involve progressive white and gray matter atrophy. It is also relevant that elevated immune-inflammatory signaling has long been recognized as an etiological mechanism in cardiovascular disease, a primary cause of excess premature mortality in patients with mood disorders.

Although extant evidence suggests that elevated immune-inflammatory signaling may represent a mechanism central to the pathophysiology of mood disorders, more definitive evaluation of the etiological relevance of this mechanism is required to establish it as a risk factor versus a risk marker. Unlike a risk marker, a risk factor implies a causal link with the illness, correction of which reduces the risk of developing the disorder. Therefore, determination of whether early normalization of elevated immune-inflammatory signaling can prevent or delay illness onset (i.e., primary prevention) will be required to evaluate risk factor status. Initial support for this approach is provided by a primary prevention trial finding that increasing dietary LC*n*-3 fatty acid intake prevented or delayed the onset of psychosis in ultra-high-risk adolescents [306]. Although this study did not examine markers of immune-inflammatory signaling to evaluate this mechanism as a response mediator, analogous primary prevention trials examining markers of immune-inflammatory status in subjects at elevated risk for developing mood disorders (i.e., having a biological parent with BD) are feasible. However, the potential long time lag between the initial emergence of mood symptoms and the first manic episode [7], and the potential for never developing mood symptoms, in youth with familial risk suggest that an alternate approach is needed to expedite elucidation of risk and resilience factors. In this regard, the IFN-α treatment paradigm may be ideally suited to prospectively and retrospectively evaluate candidate risk and resilience factors associated with mood dysregulation in response to elevated immune-inflammatory signaling in human subjects.

In view of evidence suggesting that anti-inflammatory and/or immunosuppressive agents augment the therapeutic efficacy of efficacious medications used in the treatment of mood dysregulation, it will be of considerable interest to evaluate whether anti-inflammatory agents are efficacious as monotherapy. Indeed, potential adverse metabolic effects associated with chronic treatment with conventional mood-stabilizer and atypical antipsychotic medications support a need to identify alternate treatments. Initial support is provided by the finding that LC*n*-3 fatty acid monotherapy significantly reduced depression symptom severity in pediatric and adolescent MDD patients [307]. Although this study did not evaluate markers of immune-inflammatory signaling, it suggests that an anti-

inflammatory agent by itself is sufficient to reduce mood symptom dysregulation. Furthermore, because the initial onset of mood disorders most frequently occurs during childhood and adolescence, it will be of interest to elucidate how elevated immune-inflammatory signaling impacts dynamic changes in both regressive (synaptic pruning) and progressive (i.e., myelination) cellular events observed in typically developing adolescents. For example, a prospective longitudinal neuroimaging trial could evaluate whether immune-inflammatory status is a significant predictor of progressive white and gray matter volume deterioration observed in subjects with or at high risk for developing mood disorders, and whether anti-inflammatory and/or immunosuppressive agents can mitigate these pathological brain changes.

Evidence suggesting that elevated immune-inflammatory signaling is relevant to the pathoetiology of mood disorders also suggests that targeting specific signaling molecules within this pathway may lead to the development of improved treatments. Indeed, reverse pharmacology studies suggest that downregulation of PLA_2 and COX-2 enzymes may be a mechanism of action relevant to the therapeutic actions of mood-stabilizer and atypical antipsychotic medications, and selective COX-2 inhibitors including rofecoxib or celecoxib have been found to augment the therapeutic efficacy of mood-stabilizer, atypical antipsychotic and antidepressant medications. There are a number of TNF-α antagonists that are approved by the US FDA for the treatment of conditions associated with elevated immune-inflammatory signaling (i.e., rheumatoid arthritis [308]), and preliminary studies suggest that the TNF-α antagonist etanercept may reduce depressive symptoms [309,310]. However, developing these candidates into viable treatment options will require rigorous evaluation of their long-term safety and tolerability profiles. Indeed, rofecoxib (Vioxx™) was withdrawn worldwide in 2004 because of risk of cardiovascular events, and a prospective community-based longitudinal study found that adjunctive treatment with COX-2 inhibitors was associated with a significant worsening of illness course in antipsychotic-treated patients [311]. Moreover, a case report suggests that TNF-α antagonists may increase risk of manic switching [312].

An alternate approach to targeting and treating elevated immune-inflammatory signaling in mood disorders is through the manipulation of immune cell, membrane, fatty acid composition. For example, clinical studies have found that dietary-induced elevations in immune cell LC*n*-3 fatty acid composition reduces immune-inflammatory signaling activity in human subjects [25]. This approach may be particularly well-suited for MDD and BD patients who exhibit low LC*n*-3 fatty acid status and therefore corrects a candidate etiological mechanism. Moreover, the established long-term safety profile of LC*n*-3 fatty acid supplementation, as well as demonstrated benefits for cardiovascular health, suggest that normalizing or increasing LC*n*-3 fatty acid status may represent a rational first-line approach for the long-term stabilization of immune-inflammatory signaling in mood disorders. Increasing LC*n*-3 fatty acid status to levels found in healthy subjects in Japan, where the life-time prevalence rates of MDD and BD are among the lowest worldwide, may afford increased resilience to dysregulated immune-inflammatory signaling. In view of data demonstrating that aspirin promotes the biosynthesis of potent inflammation-resolving metabolites of LC*n*-3 fatty acids (i.e., resolvins) [28,29], it will also be of interest to evaluate the therapeutic efficacy of combined treatment with aspirin and LC*n*-3 fatty acids.

Five-year view

Although the preponderance of evidence supports the proposition that elevated immune-inflammatory signaling is a pathogenic mechanism in mood disorders, additional research is needed to translate this evidence into improved treatments. In this review, the authors have highlighted several potential genetic and environmental factors that may represent candidate

targets for the development of novel anti-inflammatory and/or immuno-suppressive agents. However, additional prospective intervention research is needed to elucidate whether targeting these risk factors can provide a treatment that has superior efficacy and/or tolerability to conventional treatments. The development and evaluation of new anti-inflammatory and/or immunosuppressive agents that target different components of the immune-inflammatory signaling pathway has the potential to not only provide greater insight into pathogenic mechanisms but also novel treatment options. However, more research is needed to better define the mechanisms mediating elevated immune-inflammatory signaling and mood dysregulation, and neuroimaging techniques may aid in determining the relationship between peripheral measures of immune-inflammatory signaling and functional cortical pathology associated in mood disorders. For example, a positron emission tomography study found that regional brain arachidonic acid metabolism was elevated in patients with Alzheimer's disease [313], and this approach could be adopted for patients with mood disorders.

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Key issues

- Convergent translational evidence has implicated elevated immune-inflammatory signaling in the pathophysiology of mood disorders.
- Both genetic and environmental factors including diet may contribute to elevated immune-inflammatory signaling in mood disorders.
- Emerging data suggest that medications that are efficacious in the treatment of mood disorders downregulate immune-inflammatory signaling, and that adjunctive treatment with anti-inflammatory agents, including long-chain omega-3 fatty acids, augment treatment response.
- Elevated immune-inflammatory signaling may contribute to mood dysregulation by reducing frontal-limbic white and gray matter structural and functional integrity and/or altering serotonin neurotransmission.
- Elevated immune-inflammatory signaling represents a new therapeutic target for developing improved treatments for mood disorders.

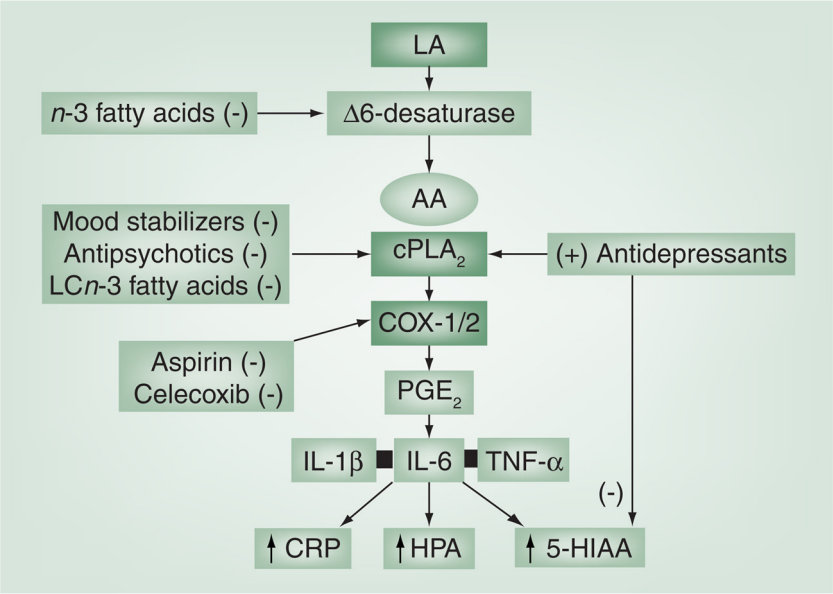

Figure 1. Simplified diagram illustrating the proposed immune-inflammatory signaling pathway implicated in the pathoetiology of mood disorders

The first and rate-limiting step in the biosynthesis of AA (20:4*n*-6) from dietary LA (18:2*n*-6) is Δ6-desaturase. Phospholipid-bound AA is mobilized by $cPLA_2$, and free AA may be metabolized by COX-1 and -2 enzymes to produce PGH_2 and PGE_2. PGE_2 stimulates the biosynthesis of IL-6, and proinflammatory cytokines including IL-1β, IL-6 and TNF-α stimulate the biosynthesis of the acute-phase protein CRP, increase HPA-axis activity and reactivity, and serotonin metabolism (5-HIAA). This proinflammatory signaling pathway is downregulated (−) by dietary *n*-3 fatty acids (i.e., α-linolenic acid), which competes with and decrease Δ6-desaturase-mediated LA→AA biosynthesis. Mood-stabilizer and atypical antipsychotic medications, as well as LC*n*-3 fatty acids, decrease PLA_2-mediated AA mobilization from phospholipids, and aspirin and celecoxib decrease COX-mediated PGE_2 biosynthesis. Different antidepressant medications have been found to augment PLA_2-mediated AA turnover, without altering COX enzyme activity or PGE_2 production, and to downegulate serotonin metabolism (5-HIAA).

5-HIAA: 5-Hydroxyindoleacetic acid; AA: Arachidonic acid; COX: Cyclooxygenase; $cPLA_2$: Calcium-dependant phospholipase A_2; CRP: C-reactive protein; LA: Linoleic acid; LC: Long-chain; PG: Prostaglandin; n-3: Omega 3.

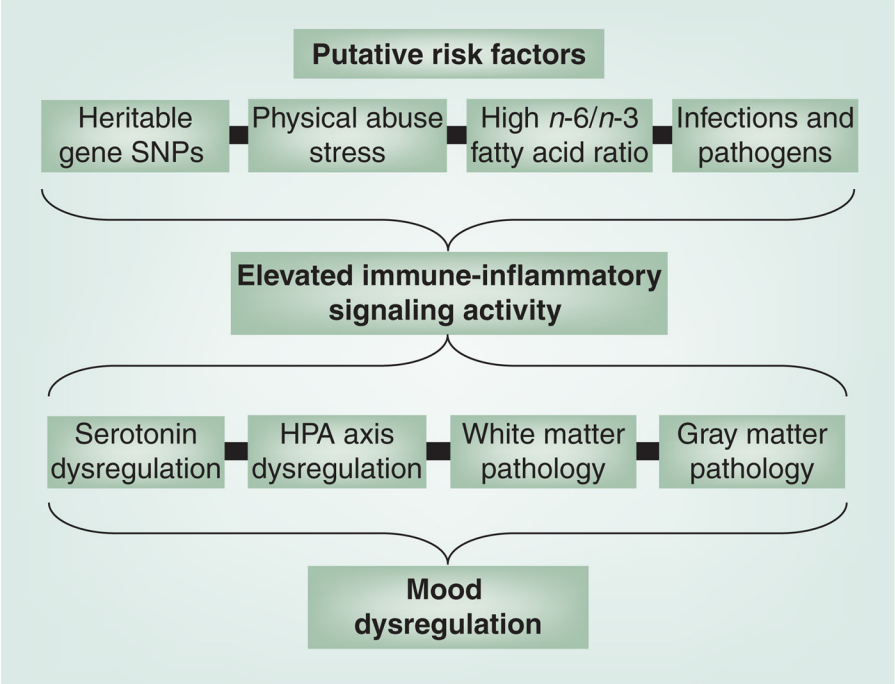

Figure 2. Diagram illustrating putative risk factors for elevated immune-inflammatory signaling and intermediate pathogenic mechanisms, which together are thought to contribute to mood dysregulation

SNP: Single-nucleotide polymorphism; *n*-3/6: Omega 3/6.