



Published in final edited form as:

*Expert Rev Neurother.* 2012 September ; 12(9): 1143–1161. doi:10.1586/ern.12.98.

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

Robert K McNamara<sup>1,\*</sup> and Francis E Lotrich<sup>2</sup>

<sup>1</sup>Department of Psychiatry, Division of Bipolar Disorders Research, University of Cincinnati College of Medicine, Cincinnati, OH, USA

<sup>2</sup>Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

### 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

---

© 2012 Expert Reviews Ltd

\* Author for correspondence: Tel.: +1 513 558 5601, Fax: +1 513 558 4805, robert.mcnamara@uc.edu.

For reprint orders, please contact reprints@expert-reviews.com

### Financial & competing interests disclosure

This work was supported in part by NIH grants MH083924 and AG03617, and a NARSAD Independent Investigator Award to RK McNamara and MH090250 to FE Lotrich. RK McNamara has received research support from Martek Biosciences Inc., Inflammation Research Foundation, Ortho-McNeil Janssen, AstraZeneca and Eli Lilly, and is a member of the Inflammation Research Foundation scientific advisory board. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

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<sub>2</sub> (cPLA<sub>2</sub>), and free arachidonic acid is a substrate for cyclooxygenase (COX)-mediated biosynthesis of prostaglandins (i.e., PGH<sub>2</sub>), thromboxanes and prostacyclins, as well as lipoxygenase-mediated biosynthesis of leukotrienes. COX-generated PGH<sub>2</sub> is converted to PGE<sub>2</sub> via PGE synthase, and PGE<sub>2</sub> stimulates the biosynthesis of downstream proinflammatory cytokines including IL-6 at the level of transcription [19–21]. Proinflammatory cytokines including IL-6, IL-1 $\beta$  and TNF- $\alpha$  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<sub>2</sub> levels in the saliva, plasma or CSF of MDD patients [30–34], and that PGE<sub>2</sub> 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<sub>2</sub> 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- $\alpha$ , and that there were no significant differences for other proinflammatory (IL-1 $\beta$ , IL-2, IFN- $\gamma$ ) 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<sub>2</sub> activity was elevated in BD patients [51]. Consistent with elevated PLA<sub>2</sub>-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<sub>2</sub> levels [53]. The majority of case–control studies have found that BD patients exhibit greater IL-6, IL-6R, IL-2R, IL-1 $\beta$  and/or TNF- $\alpha$  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- $\alpha$ , 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 complement 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-1 $\beta$ , lower IL-6 and no change in TNF- $\alpha$  [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-1 $\beta$  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<sub>2</sub>, 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<sub>2</sub> or calcium-independent phospholipase A<sub>2</sub> (iPLA<sub>2</sub>) in postmortem brains of predominantly lithium-treated BD patients, but did find that iPLA<sub>2</sub> activity was significantly greater in BD patients with a history of psychosis [79]. Consistent with elevated cPLA<sub>2</sub> 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-1 $\beta$  and IL-1R, but not TNF- $\alpha$ , 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- $\alpha$  expression in the frontal cortex of female suicide victims, no changes in IL-1 $\beta$ , 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-1 $\beta$ , and TNF- $\alpha$  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 LCn-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- $\alpha$  for the treatment of infectious diseases including hepatitis C. Approximately 30% of subjects receiving chronic IFN- $\alpha$  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- $\alpha$  treatment are associated with greater treatment-emergent increases in plasma IL-6 concentrations [99]. Moreover, IFN- $\alpha$  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-HIAA), 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- $\alpha$  [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- $\alpha$  receptor [104] and IL-6 [105] knockout mice exhibit reduced behavioral indices of depression. In rhesus monkeys, 4-week IFN- $\alpha$  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- $\alpha$  is associated with an enduring enhancement of behavioral, neurochemical and neuroendocrine responses to a second TNF- $\alpha$  injection [107]. Dietary-induced reductions in *n*-3 fatty acids, and associated elevations in the arachidonic acid/DHA ratio, are associated with elevated PLA<sub>2</sub> and COX-2 expression and activity in rat brain [35], elevated constitutive IL-6, TNF- $\alpha$  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<sub>2</sub> activity and proinflammatory PGE<sub>2</sub> 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 weight 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- $\alpha$  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<sub>2</sub> production in human synovial cells [147]. However, rodent studies have also found that the tricyclic desipramine, a noradrenergic reuptake inhibitor, increases IL-1 $\beta$  mRNA levels in the rat hypothalamus [148], and chronic treatment with different classes of antidepressants upregulate PLA<sub>2</sub>-mediated arachidonic acid turnover in rat brain [149,150]. Because the effects of antidepressants on PLA<sub>2</sub>-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-1 $\beta$  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<sub>2</sub>-mediated arachidonic acid mobilization from phospholipids and associated reductions in COX-2-mediated PGE<sub>2</sub> production in rat brain [151]. Consistent with reductions in cPLA<sub>2</sub>-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<sub>2</sub> production [165]. A recent study found that neuroinflammation elicited by chronic intracerebroventricular administration of the endotoxin LPS was associated with elevated central cPLA<sub>2</sub> activity and PGE<sub>2</sub> 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<sub>2</sub> 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- $\alpha$ , 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 LCn-3 fatty acids [172,173], augment the therapeutic efficacy of mood-stabilizer medications.

Atypical antipsychotic medications are high-affinity antagonists at serotonin 5-HT<sub>2A/C</sub> and dopamine D<sub>2</sub> receptors [174], both of which are positively coupled to cPLA<sub>2</sub> [175–180]. Chronic treatment with olanzapine or clozapine decreased cPLA<sub>2</sub>-mediated arachidonic acid turnover in cortical phospholipids, and decrease COX-2 activity and PGE<sub>2</sub> concentrations, in rat brain [181,182]. Preclinical studies have also found that atypical antipsychotic medications significantly attenuate greater IL-6 and TNF- $\alpha$  production in microglia cells following IFN- $\gamma$  exposure [183,184], and in mice following peripheral LPS administration [185]. Chronic risperidone normalized constitutively elevated plasma IL-6, TNF- $\alpha$  and CRP levels in LCn-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 LCn-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-1 $\beta$  or TNF- $\alpha$  [202], and chronic peripheral administration of IFN- $\alpha$  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- $\alpha$  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, adrenocorticotrophic 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-1 $\beta$  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- $\alpha$  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 adrenocorticotrophic 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<sub>2</sub> production in rat brain [166], and PGE<sub>2</sub>-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 LCn-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<sub>2</sub>, but not IL-1 $\beta$ , IL-2, IL-6 or TNF- $\alpha$ , in healthy human subjects [258], and elevated production of PGE<sub>2</sub> 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<sub>2</sub> 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- $\alpha$  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- $\alpha$  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- $\alpha$  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  $\Delta$ 6-desaturase activity (*FADS2*), and preclinical studies have found that *FADS2* deletion [280] or selective pharmacological inhibition of  $\Delta$ 6-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  $\Delta$ 6-desaturase activity estimates are correlated with proinflammatory markers including CRP [283,284]. *FADS2* haplotypes and/or  $\Delta$ 6-desaturase activity estimates have also been linked with disorders associated with immune-inflammatory dysregulation, including allergies [285,286] and cardiovascular disease [284,287]. The *FADS2* 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<sub>2</sub> 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<sub>2</sub>, and the PLA<sub>2</sub>BanI polymorphism is associated with greater platelet PLA<sub>2</sub> enzyme activity in schizophrenic patients [297]. Genetic association studies have found that the PLA<sub>2</sub> BanI polymorphism may be associated with MDD, but not BD [298–300], and a recent prospective study found that the PLA<sub>2</sub> BanI polymorphism was associated with more somatic symptoms of depression following IFN- $\alpha$  treatment [301]. Genetic studies have also identified a putative association between polymorphisms in IL-1 $\beta$  [302] and the TNF- $\alpha$  promoter [303–305] in BD. The TNF- $\alpha$  polymorphism is also associated with more labile anger in subjects receiving chronic IFN- $\alpha$  therapy [97]. Moreover, a COX-2 polymorphism was associated with increase the risk of developing depression in response to IFN- $\alpha$  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-1 $\beta$  and TNF- $\alpha$ , 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- $\alpha$  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<sub>2</sub> 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- $\alpha$  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- $\alpha$  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<sup>TM</sup>) 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- $\alpha$  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 LCn-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 LCn-3 fatty acid status and therefore corrects a candidate etiological mechanism. Moreover, the established long-term safety profile of LCn-3 fatty acid supplementation, as well as demonstrated benefits for cardiovascular health, suggest that normalizing or increasing LCn-3 fatty acid status may represent a rational first-line approach for the long-term stabilization of immune-inflammatory signaling in mood disorders. Increasing LCn-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 LCn-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 LCn-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.

## References

Papers of special note have been highlighted as:

- of interest
  - of considerable interest
1. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet*. 1997; 349(9063):1436–1442. [PubMed: 9164317]
  2. WHO International Consortium in Psychiatric Epidemiology. World Health Organization Cross-national comparisons of the prevalences and correlates of mental disorders. *Bull World Health Organ*. 2000; 78:413–426. [PubMed: 10885160]
  3. Kessler RC, Merikangas KR, Wang PS. Prevalence, comorbidity, and service utilization for mood disorders in the United States at the beginning of the 21st Century. *Annu Rev Clin Psychol*. 2007; 3:137–158. [PubMed: 17716051]
  4. Burke KC, Burke JD Jr, Rae DS, Regier DA. Comparing age at onset of major depression and other psychiatric disorders by birth cohorts in five US community populations. *Arch Gen Psychiatry*. 1991; 48(9):789–795. [PubMed: 1929768]
  5. Chengappa KN, Kupfer DJ, Frank E, et al. Relationship of birth cohort and early age at onset of illness in a bipolar disorder case registry. *Am J Psychiatry*. 2003; 160(9):1636–1642. [PubMed: 12944339]
  6. Perlis RH, Miyahara S, Marangell LB, et al. STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Biol Psychiatry*. 2004; 55(9):875–881. [PubMed: 15110730]
  7. Conus P, Ward J, Hallam KT, et al. The proximal prodrome to first-episode mania – a new target for early intervention. *Bipolar Disord*. 2008; 10(5):555–565. [PubMed: 18657240]
  8. Goodwin, FK.; Jamison, KR. *Manic-Depressive Illness*. Oxford University Press; NY, USA: 1990. p. 134-136.
  9. Trivedi MH, Lin EH, Katon WJ. Consensus recommendations for improving adherence, self-management, and outcomes in patients with depression. *CNS Spectr*. 2007; 12(8 Suppl 13):1–27. [PubMed: 17986951]
  10. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34–38 years. *J Affect Disord*. 2002; 68(2–3):167–181. [PubMed: 12063145]
  11. Osby U, Brandt L, Correia N, Ekblom A, Sparén P. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry*. 2001; 58(9):844–850. [PubMed: 11545667]

12. Ehringer MA, Rhee SH, Young S, Corley R, Hewitt JK. Genetic and environmental contributions to common psychopathologies of childhood and adolescence: a study of twins and their siblings. *J Abnorm Child Psychol.* 2006; 34(1):1–17. [PubMed: 16465480]
13. Merikangas KR, Chakravarti A, Moldin SO, et al. Future of genetics of mood disorders research. *Biol Psychiatry.* 2002; 52(6):457–477. [PubMed: 12361664]
14. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry.* 2000; 157(10):1552–1562. [PubMed: 11007705]
15. Farmer A, Elkin A, McGuffin P. The genetics of bipolar affective disorder. *Curr Opin Psychiatry.* 2007; 20(1):8–12. [PubMed: 17143075]
16. Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. *Am J Med Genet C Semin Med Genet.* 2003; 123C(1):48–58. [PubMed: 14601036]
17. Taylor L, Faraone SV, Tsuang MT. Family, twin, and adoption studies of bipolar disease. *Curr Psychiatry Rep.* 2002; 4(2):130–133. [PubMed: 11914174]
18. Weissman MM, Bland RC, Canino GJ, et al. Cross-national epidemiology of major depression and bipolar disorder. *JAMA.* 1996; 276(4):293–299. [PubMed: 8656541]
19. Portanova JP, Zhang Y, Anderson GD, et al. Selective neutralization of prostaglandin E2 blocks inflammation, hyperalgesia, and interleukin-6 production in vivo. *J Exp Med.* 1996; 184(3):883–891. [PubMed: 9064348]
20. Anderson GD, Hauser SD, McGarity KL, Bremer ME, Isakson PC, Gregory SA. Selective inhibition of cyclooxygenase (COX)-2 reverses inflammation and expression of COX-2 and interleukin-6 in rat adjuvant arthritis. *J Clin Invest.* 1996; 97(11):2672–2679. [PubMed: 8647962]
21. Wang P, Zhu F, Konstantopoulos K. Prostaglandin E2 induces interleukin-6 expression in human chondrocytes via cAMP/protein kinase A- and phosphatidylinositol 3-kinase-dependent NF-kappaB activation. *Am J Physiol, Cell Physiol.* 2010; 298(6):C1445–C1456. [PubMed: 20457835]
22. Castell JV, Gómez-Lechón MJ, David M, et al. Interleukin-6 is the major regulator of acute-phase protein synthesis in adult human hepatocytes. *FEBS Lett.* 1989; 242(2):237–239. [PubMed: 2464504]
23. Li SP, Liu TY, Goldman ND. cis-acting elements responsible for interleukin-6 inducible C-reactive protein gene expression. *J Biol Chem.* 1990; 265(7):4136–4142. [PubMed: 2154496]
24. Li SP, Goldman ND. Regulation of human C-reactive protein gene expression by two synergistic IL-6 responsive elements. *Biochemistry.* 1996; 35(28):9060–9068. [PubMed: 8703909]
25. Calder PC. The relationship between the fatty acid composition of immune cells and their function. *Prostaglandins Leukot Essent Fatty Acids.* 2008; 79(3–5):101–108. [PubMed: 18951005]
26. Bazan NG, Calandria JM, Serhan CN. Rescue and repair during photoreceptor cell renewal mediated by docosahexaenoic acid-derived neuroprotectin D1. *J Lipid Res.* 2010; 51(8):2018–2031. [PubMed: 20382842]
27. Groeger AL, Cipollina C, Cole MP, et al. Cyclooxygenase-2 generates anti-inflammatory mediators from omega-3 fatty acids. *Nat Chem Biol.* 2010; 6(6):433–441. [PubMed: 20436486]
28. Serhan CN. Novel lipid mediators and resolution mechanisms in acute inflammation: to resolve or not? *Am J Pathol.* 2010; 177(4):1576–1591. [PubMed: 20813960]
- 29•• Hong S, Gronert K, Devchand PR, Moussignac RL, Serhan CN. Novel docosatrienes and 17S-resolvins generated from docosahexaenoic acid in murine brain, human blood, and glial cells. Autacoids in anti-inflammation. *J Biol Chem.* 2003; 278(17):14677–14687. Seminal discovery of potent anti-inflammatory and inflammation resolving properties of metabolites of the long-chain fatty acid docosahexaenoic acid. [PubMed: 12590139]
30. Calabrese JR, Skwerer RG, Barna B, et al. Depression, immunocompetence, and prostaglandins of the E series. *Psychiatry Res.* 1986; 17(1):41–47. [PubMed: 2935897]
- 31•. Lieb J, Karmali R, Horrobin D. Elevated levels of prostaglandin E2 and thromboxane B2 in depression. *Prostaglandins Leukot Med.* 1983; 10(4):361–367. Early discovery of elevated levels of the proinflammatory arachidonic acid derivative prostaglandin E2 in patients with depression. [PubMed: 6574523]
32. Nishino S, Ueno R, Ohishi K, Sakai T, Hayaishi O. Salivary prostaglandin concentrations: possible state indicators for major depression. *Am J Psychiatry.* 1989; 146(3):365–368. [PubMed: 2627202]

33. Ohishi K, Ueno R, Nishino S, Sakai T, Hayaishi O. Increased level of salivary prostaglandins in patients with major depression. *Biol Psychiatry*. 1988; 23(4):326–334. [PubMed: 3422573]
34. Linnoila M, Whorton AR, Rubinow DR, Cowdry RW, Ninan PT, Waters RN. CSF prostaglandin levels in depressed and schizophrenic patients. *Arch Gen Psychiatry*. 1983; 40(4):405–406. [PubMed: 6838321]
35. Rao JS, Ertley RN, DeMar JC Jr, Rapoport SI, Bazinet RP, Lee HJ. Dietary *n*-3 PUFA deprivation alters expression of enzymes of the arachidonic and docosahexaenoic acid cascades in rat frontal cortex. *Mol Psychiatry*. 2007; 12(2):151–157. [PubMed: 16983392]
36. Lin PY, Huang SY, Su KP. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. *Biol Psychiatry*. 2010; 68(2):140–147. [PubMed: 20452573]
37. Adams PB, Lawson S, Sanigorski A, Sinclair AJ. Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. *Lipids*. 1996; 31(Suppl):S157–S161. [PubMed: 8729112]
38. Conklin SM, Manuck SB, Yao JK, Flory JD, Hibbeln JR, Muldoon MF. High omega-6 and low omega-3 fatty acids are associated with depressive symptoms and neuroticism. *Psychosom Med*. 2007; 69(9):932–934. [PubMed: 17991818]
39. Maes M, Smith R, Christophe A, Cosyns P, Desnyder R, Meltzer H. Fatty acid composition in major depression: decreased omega-3 fractions in cholesteryl esters and increased C20: 4 omega 6/ C20:5 omega-3 ratio in cholesteryl esters and phospholipids. *J Affect Disord*. 1996; 38(1):35–46. [PubMed: 8735157]
40. McNamara RK, Jandacek R, Rider T, Tso P, Dwivedi Y, Pandey GN. Selective deficits in erythrocyte docosahexaenoic acid composition in adult patients with bipolar disorder and major depressive disorder. *J Affect Disord*. 2010; 126(1–2):303–311. [PubMed: 20413162]
41. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010; 67(5):446–457. [PubMed: 20015486]
42. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009; 71(2):171–186. [PubMed: 19188531]
43. Kling MA, Alesci S, Csako G, et al. Sustained low-grade proinflammatory state in unmedicated, remitted women with major depressive disorder as evidenced by elevated serum levels of the acute-phase proteins C-reactive protein and serum amyloid A. *Biol Psychiatry*. 2007; 62(4):309–313. [PubMed: 17178112]
44. Kop WJ, Gottdiener JS, Tangen CM, et al. Inflammation and coagulation factors in persons >65 years of age with symptoms of depression but without evidence of myocardial ischemia. *Am J Cardiol*. 2002; 89(4):419–424. [PubMed: 11835923]
45. Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology*. 2000; 22(4):370–379. [PubMed: 10700656]
46. Penninx BW, Kritchovsky SB, Yaffe K, et al. Inflammatory markers and depressed mood in older persons: results from the Health, Aging and Body Composition study. *Biol Psychiatry*. 2003; 54(5):566–572. [PubMed: 12946885]
47. Danner M, Kasl SV, Abramson JL, Vaccarino V. Association between depression and elevated C-reactive protein. *Psychosom Med*. 2003; 65(3):347–356. [PubMed: 12764206]
48. Ford DE, Erlinger TP. Depression and C-reactive protein in US adults: data from the Third National Health and Nutrition Examination Survey. *Arch Intern Med*. 2004; 164(9):1010–1014. [PubMed: 15136311]
49. Liukkonen T, Silvennoinen–Kassinen S, Jokelainen J, et al. The association between C-reactive protein levels and depression: Results from the northern Finland 1966 birth cohort study. *Biol Psychiatry*. 2006; 60(8):825–830. [PubMed: 16616729]
50. Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. *J Clin Psychiatry*. 2009; 70(8):1078–1090. [PubMed: 19497250]
51. Noponen M, Sanfilippo M, Samanich K, et al. Elevated PLA2 activity in schizophrenics and other psychiatric patients. *Biol Psychiatry*. 1993; 34(9):641–649. [PubMed: 8292693]

52. Chiu CC, Huang SY, Su KP, et al. Polyunsaturated fatty acid deficit in patients with bipolar mania. *Eur Neuropsychopharmacol*. 2003; 13(2):99–103. [PubMed: 12650953]
53. Sublette ME, Bosetti F, DeMar JC, et al. Plasma free polyunsaturated fatty acid levels are associated with symptom severity in acute mania. *Bipolar Disord*. 2007; 9(7):759–765. [PubMed: 17988367]
54. Brietzke E, Stertz L, Fernandes BS, et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. *J Affect Disord*. 2009; 116(3):214–217. [PubMed: 19251324]
55. Maes M, Bosmans E, Calabrese J, Smith R, Meltzer HY. Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. *J Psychiatr Res*. 1995; 29(2):141–152. [PubMed: 7666381]
56. Kim YK, Jung HG, Myint AM, Kim H, Park SH. Imbalance between proinflammatory and anti-inflammatory cytokines in bipolar disorder. *J Affect Disord*. 2007; 104(1–3):91–95. [PubMed: 17434599]
57. O'Brien SM, Scully P, Scott LV, Dinan TG. Cytokine profiles in bipolar affective disorder: focus on acutely ill patients. *J Affect Disord*. 2006; 90(2–3):263–267. [PubMed: 16410025]
58. Ortiz-Domínguez A, Hernández ME, Berlanga C, et al. Immune variations in bipolar disorder: phasic differences. *Bipolar Disord*. 2007; 9(6):596–602. [PubMed: 17845274]
59. Breunis MN, Kupka RW, Nolen WA, et al. High numbers of circulating activated T cells and raised levels of serum IL-2 receptor in bipolar disorder. *Biol Psychiatry*. 2003; 53(2):157–165. Seminal discovery of elevated immune signaling in patients with bipolar disorder. [PubMed: 12547472]
60. Padmos RC, Hillegers MH, Knijff EM, et al. A discriminating messenger RNA signature for bipolar disorder formed by an aberrant expression of inflammatory genes in monocytes. *Arch Gen Psychiatry*. 2008; 65(4):395–407. [PubMed: 18391128]
61. Tsai SY, Chen KP, Yang YY, et al. Activation of indices of cell-mediated immunity in bipolar mania. *Biol Psychiatry*. 1999; 45(8):989–994. [PubMed: 10386181]
62. Tsai SY, Yang YY, Kuo CJ, Chen CC, Leu SJ. Effects of symptomatic severity on elevation of plasma soluble interleukin-2 receptor in bipolar mania. *J Affect Disord*. 2001; 64(2–3):185–193. [PubMed: 11313085]
63. Cunha AB, Andrezza AC, Gomes FA, et al. Investigation of serum high-sensitive C-reactive protein levels across all mood states in bipolar disorder. *Eur Arch Psychiatry Clin Neurosci*. 2008; 258(5):300–304. [PubMed: 18297417]
64. Huang TL, Lin FC. High-sensitivity C-reactive protein levels in patients with major depressive disorder and bipolar mania. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007; 31(2):370–372. [PubMed: 17064834]
65. Wade AA, Kuschke RH, Wood LA, Berk M, Ichim L, Maes M. Serological observations in patients suffering from acute manic episodes. *Hum Psychopharmacol*. 2002; 17(4):175–179. [PubMed: 12404684]
66. Tsai SY, Chung KH, Wu JY, Kuo CJ, Lee HC, Huang SH. Inflammatory markers and their relationships with leptin and insulin from acute mania to full remission in bipolar disorder. *J Affect Disord*. 2012; 136(1–2):110–116. [PubMed: 21962564]
67. De Berardis D, Conti CM, Campanella D, et al. Evaluation of C-reactive protein and total serum cholesterol in adult patients with bipolar disorder. *Int J Immunopathol Pharmacol*. 2008; 21(2): 319–324. [PubMed: 18547475]
68. Dickerson F, Stallings C, Origoni A, Boronow J, Yolken R. Elevated serum levels of C-reactive protein are associated with mania symptoms in outpatients with bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007; 31(4):952–955. [PubMed: 17391822]
69. Goldstein BI, Collinger KA, Lotrich F, et al. Preliminary findings regarding proinflammatory markers and brain-derived neurotrophic factor among adolescents with bipolar spectrum disorders. *J Child Adolesc Psychopharmacol*. 2011; 21(5):479–484. [PubMed: 22040193]
70. Boufidou F, Nikolaou C, Alevizos B, Liappas IA, Christodoulou GN. Cytokine production in bipolar affective disorder patients under lithium treatment. *J Affect Disord*. 2004; 82(2):309–313. [PubMed: 15488263]

71. Padmos RC, Bekris L, Knijff EM, et al. A high prevalence of organ-specific autoimmunity in patients with bipolar disorder. *Biol Psychiatry*. 2004; 56(7):476–482. [PubMed: 15450782]
72. Kupka RW, Nolen WA, Post RM, et al. High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure. *Biol Psychiatry*. 2002; 51(4):305–311. [PubMed: 11958781]
73. Levine J, Barak Y, Chengappa KN, Rapoport A, Rebey M, Barak V. Cerebrospinal cytokine levels in patients with acute depression. *Neuropsychobiology*. 1999; 40(4):171–176. [PubMed: 10559698]
74. Stübner S, Schön T, Padberg F, et al. Interleukin-6 and the soluble IL-6 receptor are decreased in cerebrospinal fluid of geriatric patients with major depression: no alteration of soluble gp130. *Neurosci Lett*. 1999; 259(3):145–148. [PubMed: 10025579]
75. Carpenter LL, Heninger GR, Malison RT, Tyrka AR, Price LH. Cerebrospinal fluid interleukin (IL)-6 in unipolar major depression. *J Affect Disord*. 2004; 79(1–3):285–289. [PubMed: 15023509]
76. Söderlund J, Olsson SK, Samuelsson M, et al. Elevation of cerebrospinal fluid interleukin-1 $\beta$  in bipolar disorder. *J Psychiatry Neurosci*. 2011; 36(2):114–118. [PubMed: 21138659]
77. Kim HW, Rapoport SI, Rao JS. Altered arachidonic acid cascade enzymes in postmortem brain from bipolar disorder patients. *Mol Psychiatry*. 2011; 16(4):419–428. [PubMed: 20038946]
78. Maida ME, Hurley SD, Daeschner JA, Moore AH, O'Banion MK. Cytosolic prostaglandin E2 synthase (cPGES) expression is decreased in discrete cortical regions in psychiatric disease. *Brain Res*. 2006; 1103(1):164–172. [PubMed: 16806120]
79. Ross BM, Hughes B, Kish SJ, Warsh JJ. Serum calcium-independent phospholipase A2 activity in bipolar affective disorder. *Bipolar Disord*. 2006; 8(3):265–270. [PubMed: 16696828]
80. McNamara RK, Jandacek R, Rider T, et al. Deficits in docosahexaenoic acid and associated elevations in the metabolism of arachidonic acid and saturated fatty acids in the postmortem orbitofrontal cortex of patients with bipolar disorder. *Psychiatry Res*. 2008; 160(3):285–299. [PubMed: 18715653]
81. Igarashi M, Ma K, Gao F, et al. Brain lipid concentrations in bipolar disorder. *J Psychiatr Res*. 2010; 44(3):177–182. [PubMed: 19767014]
82. Dean B, Tawadros N, Scarr E, Gibbons AS. Regionally-specific changes in levels of tumour necrosis factor in the dorsolateral prefrontal cortex obtained postmortem from subjects with major depressive disorder. *J Affect Disord*. 2010; 120(1–3):245–248. [PubMed: 19446343]
83. Rao JS, Harry GJ, Rapoport SI, Kim HW. Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar-disorder patients. *Mol Psychiatry*. 2010; 15(4):384–392. [PubMed: 19488045]
84. Lindqvist D, Janelidze S, Hagell P, et al. Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. *Biol Psychiatry*. 2009; 66(3):287–292. [PubMed: 19268915]
85. Tonelli LH, Stiller J, Rujescu D, et al. Elevated cytokine expression in the orbitofrontal cortex of victims of suicide. *Acta Psychiatr Scand*. 2008; 117(3):198–206. [PubMed: 18081924]
86. Pandey GN, Rizavi HS, Ren X, et al. Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. *J Psychiatr Res*. 2012; 46(1):57–63. [PubMed: 21906753]
87. Lalovic A, Levy E, Canetti L, Sequeira A, Montoudis A, Turecki G. Fatty acid composition in postmortem brains of people who completed suicide. *J Psychiatry Neurosci*. 2007; 32(5):363–370. [PubMed: 17823652]
88. McNamara RK, Jandacek R, Rider T, et al. Fatty acid composition of the postmortem prefrontal cortex of adolescent male and female suicide victims. *Prostaglandins Leukot Essent Fatty Acids*. 2009; 80(1):19–26. [PubMed: 19064316]
89. Garland MR, Hallahan B, McNamara M, et al. Lipids and essential fatty acids in patients presenting with self-harm. *Br J Psychiatry*. 2007; 190:112–117. [PubMed: 17267926]
90. Huan M, Hamazaki K, Sun Y, et al. Suicide attempt and *n*-3 fatty acid levels in red blood cells: a case control study in China. *Biol Psychiatry*. 2004; 56(7):490–496. [PubMed: 15450784]

91. Sublette ME, Hibbeln JR, Galfalvy H, Oquendo MA, Mann JJ. Omega-3 polyunsaturated essential fatty acid status as a predictor of future suicide risk. *Am J Psychiatry*. 2006; 163(6):1100–1102. [PubMed: 16741213]
92. Capuron L, Hauser P, Hinze-Selch D, Miller AH, Neveu PJ. Treatment of cytokine-induced depression. *Brain Behav Immun*. 2002; 16(5):575–580. [PubMed: 12401471]
93. Musselman DL, Lawson DH, Gumnick JF, et al. Paroxetine for the prevention of depression induced by high-dose interferon- $\alpha$ . *N Engl J Med*. 2001; 344(13):961–966. [PubMed: 11274622]
94. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol*. 2006; 27(1):24–31. [PubMed: 16316783]
95. Dan AA, Crone C, Wise TN, et al. Anger experiences among hepatitis C patients: relationship to depressive symptoms and health-related quality of life. *Psychosomatics*. 2007; 48(3):223–229. [PubMed: 17478591]
96. Pr eau M, Marcellin F, Spire B, et al. Impaired anger control as an underappreciated side effect of treatments for chronic HCV infection in HIV–HCV coinfecting patients. *J Clin Gastroenterol*. 2008; 42(1):92–96. [PubMed: 18097297]
97. Lotrich FE, Ferrell RE, Rabinovitz M, Pollock BG. Labile anger during interferon- $\alpha$  treatment is associated with a polymorphism in tumor necrosis factor- $\alpha$ . *Clin Neuropharmacol*. 2010; 33(4): 191–197. [PubMed: 20661026]
98. Constant A, Castera L, Dantzer R, et al. Mood alterations during interferon- $\alpha$  therapy in patients with chronic hepatitis C: evidence for an overlap between manic/hypomanic and depressive symptoms. *J Clin Psychiatry*. 2005; 66(8):1050–1057. [PubMed: 16086622]
99. Prather AA, Rabinovitz M, Pollock BG, Lotrich FE. Cytokine-induced depression during IFN- $\alpha$  treatment: the role of IL-6 and sleep quality. *Brain Behav Immun*. 2009; 23(8):1109–1116. This prospective study demonstrates that elevations in IL-6 in response to repeated IFN- $\alpha$  treatment is a significant predictor of emergent depressive symptoms in human subjects. [PubMed: 19615438]
100. Raison CL, Borisov AS, Majer M, et al. Activation of central nervous system inflammatory pathways by interferon- $\alpha$ : relationship to monoamines and depression. *Biol Psychiatry*. 2009; 65(4):296–303. [PubMed: 18801471]
101. Reichenberg A, Yirmiya R, Schuld A, et al. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry*. 2001; 58(5):445–452. [PubMed: 11343523]
102. Glaser R, Robles TF, Sheridan J, Malarkey WB, Kiecolt-Glaser JK. Mild depressive symptoms are associated with amplified and prolonged inflammatory responses after influenza virus vaccination in older adults. *Arch Gen Psychiatry*. 2003; 60(10):1009–1014. [PubMed: 14557146]
103. Dantzer R, O’Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008; 9(1):46–56. [PubMed: 18073775]
104. Simen BB, Duman CH, Simen AA, Duman RS. TNF- $\alpha$  signaling in depression and anxiety: behavioral consequences of individual receptor targeting. *Biol Psychiatry*. 2006; 59(9):775–785. [PubMed: 16458261]
105. Chourbaji S, Urani A, Inta I, et al. IL-6 knockout mice exhibit resistance to stress-induced development of depression-like behaviors. *Neurobiol Dis*. 2006; 23(3):587–594. [PubMed: 16843000]
106. Felger JC, Alagbe O, Hu F, et al. Effects of interferon- $\alpha$  on rhesus monkeys: a nonhuman primate model of cytokine-induced depression. *Biol Psychiatry*. 2007; 62(11):1324–1333. [PubMed: 17678633]
107. Hayley S, Brebner K, Lacosta S, Merali Z, Anisman H. Sensitization to the effects of tumor necrosis factor- $\alpha$ : neuroendocrine, central monoamine, and behavioral variations. *J Neurosci*. 1999; 19(13):5654–5665. [PubMed: 10377371]
108. McNamara RK, Jandacek R, Rider T, Tso P, Cole-Strauss A, Lipton JW. Omega-3 fatty acid deficiency increases constitutive proinflammatory cytokine production in rats: relationship with central serotonin turnover. *Prostaglandins Leukot Essent Fatty Acids*. 2010; 83(4–6):185–191. [PubMed: 20817496]

109. Mingam R, Moranis A, Bluthé RM, et al. Uncoupling of interleukin-6 from its signalling pathway by dietary *n*-3-polyunsaturated fatty acid deprivation alters sickness behaviour in mice. *Eur J Neurosci*. 2008; 28(9):1877–1886. [PubMed: 18973601]
110. DeMar JC Jr, Ma K, Bell JM, Igarashi M, Greenstein D, Rapoport SI. One generation of *n*-3 polyunsaturated fatty acid deprivation increases depression and aggression test scores in rats. *J Lipid Res*. 2006; 47(1):172–180. [PubMed: 16210728]
111. Skelin I, Kovacevic T, Sato H, Diksic M. Upregulated arachidonic acid signalling in the olfactory bulbectomized rat model of depression. *Neurochem Int*. 2011; 58(4):483–488. [PubMed: 21211542]
112. Song C, Zhang XY, Manku M. Increased phospholipase A2 activity and inflammatory response but decreased nerve growth factor expression in the olfactory bulbectomized rat model of depression: effects of chronic ethyl-eicosapentaenoate treatment. *J Neurosci*. 2009; 29(1):14–22. [PubMed: 19129380]
113. Green P, Gispán-Herman I, Yadid G. Increased arachidonic acid concentration in the brain of Flinders Sensitive Line rats, an animal model of depression. *J Lipid Res*. 2005; 46(6):1093–1096. [PubMed: 15805551]
114. Zakynthinos E, Pappa N. Inflammatory biomarkers in coronary artery disease. *J Cardiol*. 2009; 53(3):317–333. [PubMed: 19477372]
115. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group Fragmin during Instability in Coronary Artery Disease. *N Engl J Med*. 2000; 343(16):1139–1147. [PubMed: 11036119]
116. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997; 336(14):973–979. [PubMed: 9077376]
117. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation*. 2000; 101(15):1767–1772. [PubMed: 10769275]
118. Ozdemir O, Gundogdu F, Karakelleoglu S, et al. Comparison of serum levels of inflammatory markers and allelic variant of interleukin-6 in patients with acute coronary syndrome and stable angina pectoris. *Coron Artery Dis*. 2008; 19(1):15–19. [PubMed: 18281810]
119. Lindmark E, Diderholm E, Wallentin L, Siegbahn A. Relationship between interleukin-6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or noninvasive strategy. *JAMA*. 2001; 286(17):2107–2113. [PubMed: 11694151]
120. Harris WS. The omega-3 index as a risk factor for coronary heart disease. *Am J Clin Nutr*. 2008; 87(6):1997S–2002S. [PubMed: 18541601]
121. McNamara RK. Membrane omega-3 fatty acid deficiency as a preventable risk factor for comorbid coronary heart disease in major depressive disorder. *Cardiovasc Psychiatry Neurol*. 2009; 9:1–13.
122. McElroy SL, Frye MA, Suppes T, et al. Correlates of overweight and obesity in 644 patients with bipolar disorder. *J Clin Psychiatry*. 2002; 63(3):207–213. [PubMed: 11926719]
123. Fagiolini A, Frank E, Houck PR, et al. Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. *J Clin Psychiatry*. 2002; 63(6):528–533. [PubMed: 12088166]
124. Fagiolini A, Frank E, Scott JA, Turkin S, Kupfer DJ. Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. *Bipolar Disord*. 2005; 7(5):424–430. [PubMed: 16176435]
125. Wang PW, Sachs GS, Zarate CA, et al. Overweight and obesity in bipolar disorders. *J Psychiatr Res*. 2006; 40(8):762–764. [PubMed: 16516926]
126. Fiedorowicz JG, Palagummi NM, Forman-Hoffman VL, Miller DD, Haynes WG. Elevated prevalence of obesity, metabolic syndrome, and cardiovascular risk factors in bipolar disorder. *Ann Clin Psychiatry*. 2008; 20(3):131–137. [PubMed: 18633739]
127. Hansen D, Dendale P, Beelen M, et al. Plasma adipokine and inflammatory marker concentrations are altered in obese, as opposed to nonobese, Type 2 diabetes patients. *Eur J Appl Physiol*. 2010; 109(3):397–404. [PubMed: 20131064]

128. Stelzer I, Zelzer S, Raggam RB, et al. Link between leptin and interleukin-6 levels in the initial phase of obesity related inflammation. *Transl Res*. 2012; 159(2):118–124. [PubMed: 22243796]
129. Goodwin RD, Jacobi F, Thefeld W. Mental disorders and asthma in the community. *Arch Gen Psychiatry*. 2003; 60(11):1125–1130. [PubMed: 14609888]
130. Hetrick S, Merry S, McKenzie J, Sindahl P, Proctor M. Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. *Cochrane Database Syst Rev*. 2007; 3:CD004851. [PubMed: 17636776]
131. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry*. 2006; 63(3):332–339. [PubMed: 16520440]
132. Baumer FM, Howe M, Gallelli K, Simeonova DI, Hallmayer J, Chang KD. A pilot study of antidepressant-induced mania in pediatric bipolar disorder: characteristics, risk factors, and the serotonin transporter gene. *Biol Psychiatry*. 2006; 60(9):1005–1012. [PubMed: 16945343]
133. Cicero D, El-Mallakh RS, Holman J, Robertson J. Antidepressant exposure in bipolar children. *Psychiatry*. 2003; 66(4):317–322. [PubMed: 14964693]
134. Faedda GL, Baldessarini RJ, Glovinsky IP, Austin NB. Treatment-emergent mania in pediatric bipolar disorder: a retrospective case review. *J Affect Disord*. 2004; 82(1):149–158. [PubMed: 15465590]
135. Martin A, Young C, Leckman JF, Mukonoweshuro C, Rosenheck R, Leslie D. Age effects on antidepressant-induced manic conversion. *Arch Pediatr Adolesc Med*. 2004; 158(8):773–780. [PubMed: 15289250]
136. Findling RL, Frazier TW, Youngstrom EA, et al. Double-blind, placebo-controlled trial of divalproex monotherapy in the treatment of symptomatic youth at high risk for developing bipolar disorder. *J Clin Psychiatry*. 2007; 68(5):781–788. [PubMed: 17503990]
137. Geller B, Cooper TB, Zimmerman B, et al. Lithium for prepubertal depressed children with family history predictors of future bipolarity: a double-blind, placebo-controlled study. *J Affect Disord*. 1998; 51(2):165–175. [PubMed: 10743849]
138. Verrotti A, la Torre R, Trotta D, Mohn A, Chiarelli F. Valproate-induced insulin resistance and obesity in children. *Horm Res*. 2009; 71(3):125–131. [PubMed: 19188736]
139. Fraguas D, Correll CU, Merchán-Naranjo J, et al. Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: comprehensive review of prospective head-to-head and placebo-controlled comparisons. *Eur Neuropsychopharmacol*. 2011; 21(8):621–645. [PubMed: 20702068]
140. Smith LA, Cornelius V, Warnock A, Bell A, Young AH. Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. *Bipolar Disord*. 2007; 9(4):394–412. [PubMed: 17547586]
141. Scherk H, Pajonk FG, Leucht S. Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trials. *Arch Gen Psychiatry*. 2007; 64(4):442–455. [PubMed: 17404121]
142. Bond DJ, Lam RW, Yatham LN. Divalproex sodium versus placebo in the treatment of acute bipolar depression: a systematic review and meta-analysis. *J Affect Disord*. 2010; 124(3):228–234. [PubMed: 20044142]
143. Correll CU, Manu P, Olshansky V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009; 302(16):1765–1773. [PubMed: 19861668]
144. Castanon N, Leonard BE, Neveu PJ, Yirmiya R. Effects of antidepressants on cytokine production and actions. *Brain Behav Immun*. 2002; 16(5):569–574. [PubMed: 12401470]
145. Kenis G, Maes M. Effects of antidepressants on the production of cytokines. *Int J Neuropsychopharmacol*. 2002; 5(4):401–412. [PubMed: 12466038]
146. Yirmiya R, Pollak Y, Barak O, et al. Effects of antidepressant drugs on the behavioral and physiological responses to lipopolysaccharide (LPS) in rodents. *Neuropsychopharmacology*. 2001; 24(5):531–544. [PubMed: 11282253]
147. Yaron I, Shirazi I, Judovich R, Levartovsky D, Caspi D, Yaron M. Fluoxetine and amitriptyline inhibit nitric oxide, prostaglandin E2, and hyaluronic acid production in human synovial cells and synovial tissue cultures. *Arthritis Rheum*. 1999; 42(12):2561–2568. [PubMed: 10616001]

148. Porterfield VM, Zimomra ZR, Caldwell EA, Camp RM, Gabella KM, Johnson JD. Rat strain differences in restraint stress-induced brain cytokines. *Neuroscience*. 2011; 188:48–54. [PubMed: 21605631]
149. Lee HJ, Rao JS, Ertley RN, Chang L, Rapoport SI, Bazinet RP. Chronic fluoxetine increases cytosolic phospholipase A(2) activity and arachidonic acid turnover in brain phospholipids of the unanesthetized rat. *Psychopharmacology (Berl)*. 2007; 190(1):103–115. [PubMed: 17093977]
150. Lee HJ, Rao JS, Chang L, Rapoport SI, Kim HW. Chronic imipramine but not bupropion increases arachidonic acid signaling in rat brain: is this related to ‘switching’ in bipolar disorder? *Mol Psychiatry*. 2010; 15(6):602–614. [PubMed: 18982003]
151. Rao JS, Lee HJ, Rapoport SI, Bazinet RP. Mode of action of mood stabilizers: is the arachidonic acid cascade a common target? *Mol Psychiatry*. 2008; 13(6):585–596. [PubMed: 18347600]
152. Post RM, Altshuler LL, Leverich GS, et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. *Br J Psychiatry*. 2006; 189:124–131. [PubMed: 16880481]
153. Jazayeri S, Keshavarz SA, Tehrani-Doost M, et al. Effects of eicosapentaenoic acid and fluoxetine on plasma cortisol, serum interleukin-1 $\beta$  and interleukin-6 concentrations in patients with major depressive disorder. *Psychiatry Res*. 2010; 178(1):112–115. [PubMed: 20466437]
154. Maes M, Meltzer HY, Bosmans E, et al. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. *J Affect Disord*. 1995; 34(4):301–309. [PubMed: 8550956]
155. Sluzewska A, Sobieska M, Rybakowski JK. Changes in acute-phase proteins during lithium potentiation of antidepressants in refractory depression. *Neuropsychobiology*. 1997; 35(3):123–127. [PubMed: 9170116]
156. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment-resistant depression. *Cytokine*. 1997; 9(11):853–858. [PubMed: 9367546]
157. Müller N, Schwarz MJ, Dehning S, et al. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Mol Psychiatry*. 2006; 11(7):680–684. [PubMed: 16491133]
158. Musil R, Schwarz MJ, Riedel M, et al. Elevated macrophage migration inhibitory factor and decreased transforming growth factor- $\beta$  levels in major depression – no influence of celecoxib treatment. *J Affect Disord*. 2011; 134(1–3):217–225. [PubMed: 21684012]
159. Akhondzadeh S, Jafari S, Raisi F, et al. Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double-blind and placebo-controlled trial. *Depress Anxiety*. 2009; 26(7):607–611. [PubMed: 19496103]
160. Mendlewicz J, Kriwin P, Oswald P, Souery D, Alboni S, Brunello N. Shortened onset of action of antidepressants in major depression using acetylsalicylic acid augmentation: a pilot open-label study. *Int Clin Psychopharmacol*. 2006; 21(4):227–231. [PubMed: 16687994]
161. Jazayeri S, Tehrani-Doost M, Keshavarz SA, et al. Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic acid and fluoxetine, separately and in combination, in major depressive disorder. *Aust N Z J Psychiatry*. 2008; 42(3):192–198. [PubMed: 18247193]
162. Gertsik L, Poland RE, Bresee C, Rapaport MH. Omega-3 fatty acid augmentation of citalopram treatment for patients with major depressive disorder. *J Clin Psychopharmacol*. 2012; 32(1):61–64. [PubMed: 22198441]
163. Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry*. 2002; 59(10):913–919. [PubMed: 12365878]
164. McNamara RK, Sullivan J, Richtand NM. Omega-3 fatty acid deficiency augments amphetamine-induced behavioral sensitization in adult mice: prevention by chronic lithium treatment. *J Psychiatr Res*. 2008; 42(6):458–468. [PubMed: 17628596]
- 165••. Rapoport SI. Brain arachidonic and docosahexaenoic acid cascades are selectively altered by drugs, diet and disease. *Prostaglandins Leukot Essent Fatty Acids*. 2008; 79(3–5):153–156. This review describes series of elegant experiments that demonstrate that downregulation of

arachidonic acid signaling is a common mechanism of action of mood-stabilizer medications. [PubMed: 18973997]

166. Basselin M, Kim HW, Chen M, et al. Lithium modifies brain arachidonic and docosahexaenoic metabolism in rat lipopolysaccharide model of neuroinflammation. *J Lipid Res.* 2010; 51(5): 1049–1056. [PubMed: 20040630]
167. Rapoport SI, Basselin M, Kim HW, Rao JS. Bipolar disorder and mechanisms of action of mood stabilizers. *Brain Res Rev.* 2009; 61(2):185–209. [PubMed: 19555719]
168. Knijff EM, Breunis MN, Kupka RW, et al. An imbalance in the production of IL-1 $\beta$  and IL-6 by monocytes of bipolar patients: restoration by lithium treatment. *Bipolar Disord.* 2007; 9(7): 743–753. This clinical study demonstrates that elevated indices of immune-inflammation signaling activity in medication-free bipolar patients is normalized following treatment with lithium, thereby implicating this mechanism in the pathophysiology and treatment of mood symptoms. [PubMed: 17988365]
169. Rapaport MH, Guylai L, Whybrow P. Immune parameters in rapid cycling bipolar patients before and after lithium treatment. *J Psychiatr Res.* 1999; 33(4):335–340. [PubMed: 10404471]
170. Nery FG, Monkul ES, Hatch JP, et al. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. *Hum Psychopharmacol.* 2008; 23(2):87–94. [PubMed: 18172906]
171. Stolk P, Souverein PC, Wilting I, et al. Is aspirin useful in patients on lithium? A pharmacoepidemiological study related to bipolar disorder. *Prostaglandins Leukot Essent Fatty Acids.* 2010; 82(1):9–14. [PubMed: 19939659]
172. Clayton EH, Hanstock TL, Hirneth SJ, Kable CJ, Garg ML, Hazell PL. Reduced mania and depression in juvenile bipolar disorder associated with long-chain omega-3 polyunsaturated fatty acid supplementation. *Eur J Clin Nutr.* 2009; 63(8):1037–1040. [PubMed: 19156158]
173. Stoll AL, Severus WE, Freeman MP, et al. Omega-3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry.* 1999; 56(5):407–412. [PubMed: 10232294]
174. Richtand NM, Welge JA, Logue AD, Keck PE Jr, Strakowski SM, McNamara RK. Dopamine and serotonin receptor binding and antipsychotic efficacy. *Neuropsychopharmacology.* 2007; 32(8):1715–1726. [PubMed: 17251913]
175. Garcia MC, Kim HY. Mobilization of arachidonate and docosahexaenoate by stimulation of the 5-HT<sub>2A</sub> receptor in rat C6 glioma cells. *Brain Res.* 1997; 768(1–2):43–48. [PubMed: 9369299]
176. Nilsson CL, Hellstrand M, Ekman A, Eriksson E. Direct dopamine D<sub>2</sub>-receptor-mediated modulation of arachidonic acid release in transfected CHO cells without the concomitant administration of a Ca<sup>2+</sup>-mobilizing agent. *Br J Pharmacol.* 1998; 124(8):1651–1658. [PubMed: 9756380]
177. Piomelli D, Pilon C, Giros B, Sokoloff P, Martres MP, Schwartz JC. Dopamine activation of the arachidonic acid cascade as a basis for D<sub>1</sub>/D<sub>2</sub> receptor synergism. *Nature.* 1991; 353(6340):164–167. [PubMed: 1909771]
178. Qu Y, Chang L, Klaff J, Balbo A, Rapoport SI. Imaging brain phospholipase A<sub>2</sub> activation in awake rats in response to the 5-HT<sub>2A/2C</sub> agonist (+/-)2,5-dimethoxy-4-iodophenyl-2-aminopropane (DOI). *Neuropsychopharmacology.* 2003; 28(2):244–252. [PubMed: 12589377]
179. Basselin M, Chang L, Bell JM, Rapoport SI. Chronic lithium chloride administration to unanesthetized rats attenuates brain dopamine D<sub>2</sub>-like receptor-initiated signaling via arachidonic acid. *Neuropsychopharmacology.* 2005; 30(6):1064–1075. [PubMed: 15812572]
180. Bhattacharjee AK, Chang L, White L, Bazinet RP, Rapoport SI. D-amphetamine stimulates D<sub>2</sub> dopamine receptor-mediated brain signaling involving arachidonic acid in unanesthetized rats. *J Cereb Blood Flow Metab.* 2006; 26(11):1378–1388. [PubMed: 16511499]
181. Kim HW, Cheon Y, Modi HR, Rapoport SI, Rao JS. Effects of chronic clozapine administration on markers of arachidonic acid cascade and synaptic integrity in rat brain. *Psychopharmacology (Berl).* 2012; 222(4):663–674. [PubMed: 22414961]
182. Cheon Y, Park JY, Modi HR, et al. Chronic olanzapine treatment decreases arachidonic acid turnover and prostaglandin E<sub>2</sub> concentration in rat brain. *J Neurochem.* 2011; 119(2):364–376. [PubMed: 21812779]

183. Bian Q, Kato T, Monji A, et al. The effect of atypical antipsychotics, perospirone, ziprasidone and quetiapine on microglial activation induced by interferon- $\gamma$ . *Prog Neuropsychopharmacol Biol Psychiatry*. 2008; 32(1):42–48. [PubMed: 17716796]
184. Kato T, Monji A, Hashioka S, Kanba S. Risperidone significantly inhibits interferon- $\gamma$ -induced microglial activation *in vitro*. *Schizophr Res*. 2007; 92(1–3):108–115. [PubMed: 17363222]
185. Sugino H, Futamura T, Mitsumoto Y, Maeda K, Marunaka Y. Atypical antipsychotics suppress production of proinflammatory cytokines and up-regulate interleukin-10 in lipopolysaccharide-treated mice. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009; 33(2):303–307. [PubMed: 19138716]
186. McNamara RK, Jandacek R, Rider T, Tso P. Chronic risperidone normalizes elevated proinflammatory cytokine and C-reactive protein production in omega-3 fatty acid deficient rats. *Eur J Pharmacol*. 2011; 652(1–3):152–156. [PubMed: 21118685]
187. Drzyzga L, Obuchowicz E, Marcinowska A, Herman ZS. Cytokines in schizophrenia and the effects of antipsychotic drugs. *Brain Behav Immun*. 2006; 20(6):532–545. [PubMed: 16580814]
188. Akhondzadeh S, Tabatabaee M, Amini H, Ahmadi Abhari SA, Abbasi SH, Behnam B. Celecoxib as adjunctive therapy in schizophrenia: a double-blind, randomized and placebo-controlled trial. *Schizophr Res*. 2007; 90(1–3):179–185. [PubMed: 17208413]
189. Berger GE, Proffitt TM, McConchie M, et al. Ethyl-eicosapentaenoic acid in first-episode psychosis: a randomized, placebo-controlled trial. *J Clin Psychiatry*. 2007; 68(12):1867–1875. [PubMed: 18162017]
190. Arango V, Underwood MD, Mann JJ. Serotonin brain circuits involved in major depression and suicide. *Prog Brain Res*. 2002; 136:443–453. [PubMed: 12143401]
191. Vaswani M, Linda FK, Ramesh S. Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003; 27(1): 85–102. [PubMed: 12551730]
192. Rosa-Neto P, Diksic M, Okazawa H, et al. Measurement of brain regional  $\alpha$ -[ $^{11}\text{C}$ ] methyl-L-tryptophan trapping as a measure of serotonin synthesis in medication-free patients with major depression. *Arch Gen Psychiatry*. 2004; 61(6):556–563. [PubMed: 15184235]
193. Barton DA, Esler MD, Dawood T, et al. Elevated brain serotonin turnover in patients with depression: effect of genotype and therapy. *Arch Gen Psychiatry*. 2008; 65(1):38–46. [PubMed: 18180427]
194. Lundmark J, Wälinder J, Alling C, Manniche PM, Dalgaard L. The effect of paroxetine on cerebrospinal fluid concentrations of neurotransmitter metabolites in depressed patients. *Eur Neuropsychopharmacol*. 1994; 4(1):1–6. [PubMed: 7515737]
195. De Bellis MD, Geraciotti TD Jr, Altemus M, Kling MA. Cerebrospinal fluid monoamine metabolites in fluoxetine-treated patients with major depression and in healthy volunteers. *Biol Psychiatry*. 1993; 33(8–9):636–641. [PubMed: 7687151]
196. Potter WZ, Scheinin M, Golden RN, et al. Selective antidepressants and cerebrospinal fluid. Lack of specificity on norepinephrine and serotonin metabolites. *Arch Gen Psychiatry*. 1985; 42(12): 1171–1177. [PubMed: 2416297]
197. Sheline Y, Bardgett ME, Csernansky JG. Correlated reductions in cerebrospinal fluid 5-HIAA and MHPG concentrations after treatment with selective serotonin reuptake inhibitors. *J Clin Psychopharmacol*. 1997; 17(1):11–14. [PubMed: 9004051]
198. Unceta N, Barrondo S, Ruiz de Azúa I, et al. Determination of fluoxetine, norfluoxetine and their enantiomers in rat plasma and brain samples by liquid chromatography with fluorescence detection. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2007; 852(1–2):519–528.
199. McNamara RK, Able JA, Rider T, Tso P, Jandacek R. Effect of chronic fluoxetine treatment on male and female rat erythrocyte and prefrontal cortex fatty acid composition. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010; 34(7):1317–1321. [PubMed: 20655971]
200. Wang J, Dunn AJ. Mouse interleukin-6 stimulates the HPA axis and increases brain tryptophan and serotonin metabolism. *Neurochem Int*. 1998; 33(2):143–154. [PubMed: 9761458]
201. Zhang J, Terreni L, De Simoni MG, Dunn AJ. Peripheral interleukin-6 administration increases extracellular concentrations of serotonin and the evoked release of serotonin in the rat striatum. *Neurochem Int*. 2001; 38(4):303–308. [PubMed: 11137624]

202. Clement HW, Buschmann J, Rex S, et al. Effects of interferon- $\gamma$ , interleukin-1 $\beta$ , and tumor necrosis factor- $\alpha$  on the serotonin metabolism in the nucleus raphe dorsalis of the rat. *J Neural Transm.* 1997; 104(10):981–991. [PubMed: 9503251]
203. Sato T, Suzuki E, Yokoyama M, Semba J, Watanabe S, Miyaoka H. Chronic intraperitoneal injection of interferon- $\alpha$  reduces serotonin levels in various regions of rat brain, but does not change levels of serotonin transporter mRNA, nitrite or nitrate. *Psychiatry Clin Neurosci.* 2006; 60(4):499–506. [PubMed: 16884454]
204. Hayley S, Lacosta S, Merali Z, van Rooijen N, Anisman H. Central monoamine and plasma corticosterone changes induced by a bacterial endotoxin: sensitization and cross-sensitization effects. *Eur J Neurosci.* 2001; 13(6):1155–1165. [PubMed: 11285013]
205. Pariante CM, Miller AH. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biol Psychiatry.* 2001; 49(5):391–404. [PubMed: 11274650]
206. Ströhle A, Holsboer F. Stress responsive neurohormones in depression and anxiety. *Pharmacopsychiatry.* 2003; 36(Suppl 3):S207–S214. [PubMed: 14677081]
207. Beishuizen A, Thijs LG. Endotoxin and the hypothalamo–pituitary–adrenal (HPA) axis. *J Endotoxin Res.* 2003; 9(1):3–24. [PubMed: 12691614]
208. Grinevich V, Ma XM, Herman JP, Jezova D, Akmayev I, Aguilera G. Effect of repeated lipopolysaccharide administration on tissue cytokine expression and hypothalamic–pituitary–adrenal axis activity in rats. *J Neuroendocrinol.* 2001; 13(8):711–723. [PubMed: 11489088]
209. Jankord R, Zhang R, Flak JN, Solomon MB, Albertz J, Herman JP. Stress activation of IL-6 neurons in the hypothalamus. *Am J Physiol Regul Integr Comp Physiol.* 2010; 299(1):R343–R351. [PubMed: 20427720]
210. Frank MG, Miguel ZD, Watkins LR, Maier SF. Prior exposure to glucocorticoids sensitizes the neuroinflammatory and peripheral inflammatory responses to *E. coli* lipopolysaccharide. *Brain Behav Immun.* 2010; 24(1):19–30. [PubMed: 19647070]
211. Pace TW, Miller AH. Cytokines and glucocorticoid receptor signaling. Relevance to major depression. *Ann NY Acad Sci.* 2009; 1179:86–105. [PubMed: 19906234]
212. Pluess TT, Hayoz D, Berger MM, et al. Intravenous fish oil blunts the physiological response to endotoxin in healthy subjects. *Intensive Care Med.* 2007; 33(5):789–797. [PubMed: 17377770]
213. Michaeli B, Berger MM, Revelly JP, Tappy L, Chioléro R. Effects of fish oil on the neuroendocrine responses to an endotoxin challenge in healthy volunteers. *Clin Nutr.* 2007; 26(1):70–77. [PubMed: 17055120]
214. Reynolds R, Roncaroli F, Nicholas R, Radotra B, Gveric D, Howell O. The neuropathological basis of clinical progression in multiple sclerosis. *Acta Neuropathol.* 2011; 122(2):155–170. [PubMed: 21626034]
215. Chwastiak LA, Ehde DM. Psychiatric issues in multiple sclerosis. *Psychiatr Clin North Am.* 2007; 30(4):803–817. [PubMed: 17938046]
216. Chwastiak L, Ehde DM, Gibbons LE, Sullivan M, Bowen JD, Kraft GH. Depressive symptoms and severity of illness in multiple sclerosis: epidemiologic study of a large community sample. *Am J Psychiatry.* 2002; 159(11):1862–1868. [PubMed: 12411220]
217. Iacovides A, Andreoulakis E. Bipolar disorder and resembling special psychopathological manifestations in multiple sclerosis: a review. *Curr Opin Psychiatry.* 2011; 24(4):336–340. [PubMed: 21546839]
218. Scolozzi R, Boccafogli A, Tola MR, et al. T-cell phenotypic profiles in the cerebrospinal fluid and peripheral blood of multiple sclerosis patients. *J Neurol Sci.* 1992; 108(1):93–98. [PubMed: 1352538]
219. Trotter JL, Clifford DB, Anderson CB, van der Veen RC, Hicks BC, Banks G. Elevated serum interleukin-2 levels in chronic progressive multiple sclerosis. *N Engl J Med.* 1988; 318(18):1206. [PubMed: 3258957]
220. Drexhage RC, Hoogenboezem TH, Versnel MA, Berghout A, Nolen WA, Drexhage HA. The activation of monocyte and T-cell networks in patients with bipolar disorder. *Brain Behav Immun.* 2011; 25(6):1206–1213. [PubMed: 21443944]

221. Aston C, Jiang L, Sokolov BP. Transcriptional profiling reveals evidence for signaling and oligodendroglial abnormalities in the temporal cortex from patients with major depressive disorder. *Mol Psychiatry*. 2005; 10(3):309–322. [PubMed: 15303102]
222. Tkachev D, Mimmack ML, Ryan MM, et al. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet*. 2003; 362(9386):798–805. [PubMed: 13678875]
223. Regenold WT, Phatak P, Marano CM, Gearhart L, Viens CH, Hisley KC. Myelin staining of deep white matter in the dorsolateral prefrontal cortex in schizophrenia, bipolar disorder, and unipolar major depression. *Psychiatry Res*. 2007; 151(3):179–188. [PubMed: 17433451]
224. Hasan KM, Gupta RK, Santos RM, Wolinsky JS, Narayana PA. Diffusion tensor fractional anisotropy of the normal-appearing seven segments of the corpus callosum in healthy adults and relapsing-remitting multiple sclerosis patients. *J Magn Reson Imaging*. 2005; 21(6):735–743. [PubMed: 15906348]
225. Benedetti F, Absinta M, Rocca MA, et al. Tract-specific white matter structural disruption in patients with bipolar disorder. *Bipolar Disord*. 2011; 13(4):414–424. [PubMed: 21843281]
226. Heng S, Song AW, Sim K. White matter abnormalities in bipolar disorder: insights from diffusion tensor imaging studies. *J Neural Transm*. 2010; 117(5):639–654. [PubMed: 20107844]
227. Zanetti MV, Jackowski MP, Versace A, et al. State-dependent microstructural white matter changes in bipolar I depression. *Eur Arch Psychiatry Clin Neurosci*. 2009; 259(6):316–328. [PubMed: 19255710]
228. Wu F, Tang Y, Xu K, et al. Whiter matter abnormalities in medication-naive subjects with a single short-duration episode of major depressive disorder. *Psychiatry Res*. 2011; 191(1):80–83. [PubMed: 21145709]
229. Zhu X, Wang X, Xiao J, Zhong M, Liao J, Yao S. Altered white matter integrity in first-episode, treatment-naive young adults with major depressive disorder: a tract-based spatial statistics study. *Brain Res*. 2011; 1369:223–229. [PubMed: 21047498]
230. Eugster HP, Frei K, Kopf M, Lassmann H, Fontana A. IL-6-deficient mice resist myelin oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis. *Eur J Immunol*. 1998; 28(7):2178–2187. [PubMed: 9692887]
231. Mendel I, Katz A, Kozak N, Ben-Nun A, Revel M. Interleukin-6 functions in autoimmune encephalomyelitis: a study in gene-targeted mice. *Eur J Immunol*. 1998; 28(5):1727–1737. [PubMed: 9603480]
232. Stolp HB, Dziegielewska KM, Ek CJ, Potter AM, Saunders NR. Long-term changes in blood–brain barrier permeability and white matter following prolonged systemic inflammation in early development in the rat. *Eur J Neurosci*. 2005; 22(11):2805–2816. [PubMed: 16324115]
233. Stolp HB, Ek CJ, Johansson PA, et al. Factors involved in inflammation-induced developmental white matter damage. *Neurosci Lett*. 2009; 451(3):232–236. [PubMed: 19152829]
234. Tuzun F, Kumral A, Dilek M, et al. Maternal omega-3 fatty acid supplementation protects against lipopolysaccharide-induced white matter injury in the neonatal rat brain. *J Matern Fetal Neonatal Med*. 2012; 25(6):849–854. [PubMed: 21892882]
235. Ward RE, Huang W, Curran OE, Priestley JV, Michael-Titus AT. Docosahexaenoic acid prevents white matter damage after spinal cord injury. *J Neurotrauma*. 2010; 27(10):1769–1780. [PubMed: 20698757]
236. Kempton MJ, Geddes JR, Ettinger U, Williams SC, Grasby PM. Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. *Arch Gen Psychiatry*. 2008; 65(9):1017–1032. [PubMed: 18762588]
237. Kempton MJ, Salvador Z, Munafò MR, et al. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. *Arch Gen Psychiatry*. 2011; 68(7):675–690. [PubMed: 21727252]
238. Campbell LR, Pang Y, Ojeda NB, Zheng B, Rhodes PG, Alexander BT. Intracerebral lipopolysaccharide induces neuroinflammatory change and augmented brain injury in growth-restricted neonatal rats. *Pediatr Res*. 2012; 71(6):645–652. [PubMed: 22337231]
239. Hauss-Wegrzyniak B, Galons JP, Wenk GL. Quantitative volumetric analyses of brain magnetic resonance imaging from rat with chronic neuroinflammation. *Exp Neurol*. 2000; 165(2):347–354. [PubMed: 10993694]

240. Carrasco E, Casper D, Werner P. PGE(2) receptor EP1 renders dopaminergic neurons selectively vulnerable to low-level oxidative stress and direct PGE(2) neurotoxicity. *J Neurosci Res*. 2007; 85(14):3109–3117. [PubMed: 17868147]
241. Kawaguchi K, Hickey RW, Rose ME, Zhu L, Chen J, Graham SH. Cyclooxygenase-2 expression is induced in rat brain after kainate-induced seizures and promotes neuronal death in CA3 hippocampus. *Brain Res*. 2005; 1050(1–2):130–137. [PubMed: 15979590]
242. Rao JS, Kellom M, Kim HW, Rapoport SI, Reese EA. Neuroinflammation and synaptic loss. *Neurochem Res*. 2012; 37(5):903–910. [PubMed: 22311128]
243. Myint AM, Schwarz MJ, Müller N. The role of the kynurenine metabolism in major depression. *J Neural Transm*. 2012; 119(2):245–251. [PubMed: 22139324]
244. Conklin SM, Gianaros PJ, Brown SM, et al. Long-chain omega-3 fatty acid intake is associated positively with corticolimbic gray matter volume in healthy adults. *Neurosci Lett*. 2007; 421(3):209–212. [PubMed: 17574755]
245. Padmos RC, Van Baal GC, Vonk R, et al. Genetic and environmental influences on proinflammatory monocytes in bipolar disorder: a twin study. *Arch Gen Psychiatry*. 2009; 66(9):957–965. [PubMed: 19736352]
246. Pearce BD, Kruszon-Moran D, Jones JL. The relationship between *Toxoplasma gondii* infection and mood disorders in the third national health and nutrition survey. *Biol Psychiatry*. 2012; 72(4):290–295. [PubMed: 22325983]
247. Lee HC, Tsai SY, Lin HC. Seasonal variations in bipolar-disorder admissions and the association with climate: a population-based study. *J Affect Disord*. 2007; 97(1–3):61–69. [PubMed: 16890994]
248. Cassidy F, Carroll BJ. Seasonal variation of mixed and pure episodes of bipolar disorder. *J Affect Disord*. 2002; 68(1):25–31. [PubMed: 11869779]
249. Dickerson F, Stallings C, Origoni A, et al. Markers of gluten sensitivity and celiac disease in bipolar disorder. *Bipolar Disord*. 2011; 13(1):52–58. [PubMed: 21320252]
250. Post RM, Leverich GS. The role of psychosocial stress in the onset and progression of bipolar disorder and its comorbidities: the need for earlier and alternative modes of therapeutic intervention. *Dev Psychopathol*. 2006; 18(4):1181–1211. [PubMed: 17064434]
251. Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. *Proc Natl Acad Sci USA*. 2007; 104(4):1319–1324. This study demonstrates that maltreatment in childhood, which is associated with increased risk for developing mood disorders, has a long-standing effect on immune-inflammatory signaling in adulthood. [PubMed: 17229839]
252. McDade TW, Hawkley LC, Cacioppo JT. Psychosocial and behavioral predictors of inflammation in middle-aged and older adults: the Chicago health, aging, and social relations study. *Psychosom Med*. 2006; 68(3):376–381. [PubMed: 16738067]
253. Miller GE, Rohleder N, Cole SW. Chronic interpersonal stress predicts activation of pro- and anti-inflammatory signaling pathways 6 months later. *Psychosom Med*. 2009; 71(1):57–62. [PubMed: 19073750]
254. Spitzer C, Barnow S, Völzke H, et al. Association of posttraumatic stress disorder with low-grade elevation of C-reactive protein: evidence from the general population. *J Psychiatr Res*. 2010; 44(1):15–21. [PubMed: 19628221]
255. von Känel R, Hepp U, Kraemer B, et al. Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. *J Psychiatr Res*. 2007; 41(9):744–752. [PubMed: 16901505]
256. Pace TW, Mletzko TC, Alagbe O, et al. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *Am J Psychiatry*. 2006; 163(9):1630–1633. [PubMed: 16946190]
257. Blasbalg TL, Hibbeln JR, Ramsden CE, Majchrzak SF, Rawlings RR. Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th Century. *Am J Clin Nutr*. 2011; 93(5):950–962. [PubMed: 21367944]

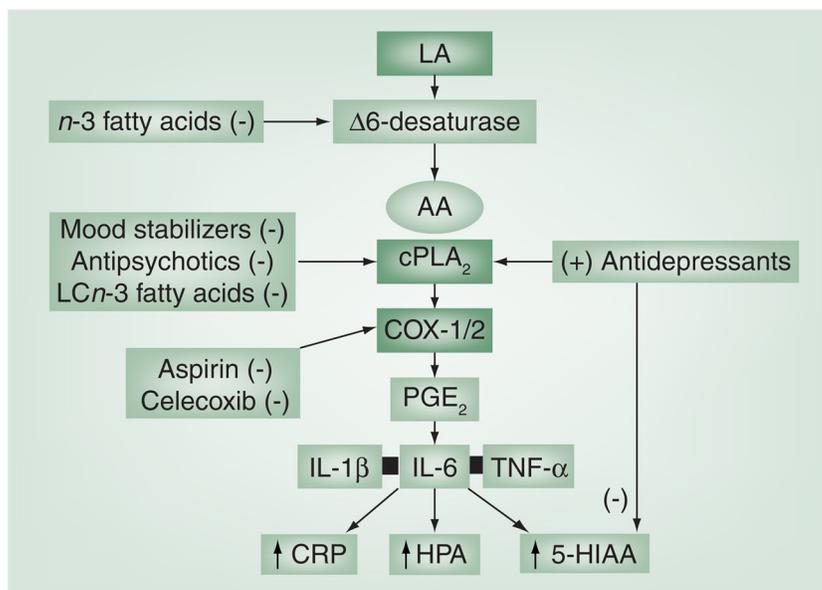
258. Kelley DS, Taylor PC, Nelson GJ, Mackey BE. Arachidonic acid supplementation enhances synthesis of eicosanoids without suppressing immune functions in young healthy men. *Lipids*. 1998; 33(2):125–130. [PubMed: 9507233]
259. Song C, Li X, Leonard BE, Horrobin DF. Effects of dietary *n*-3 or *n*-6 fatty acids on interleukin-1 $\beta$ -induced anxiety, stress, and inflammatory responses in rats. *J Lipid Res*. 2003; 44(10):1984–1991. [PubMed: 12837849]
260. Song C, Manku MS, Horrobin DF. Long-chain polyunsaturated fatty acids modulate interleukin-1 $\beta$ -induced changes in behavior, monoaminergic neurotransmitters, and brain inflammation in rats. *J Nutr*. 2008; 138(5):954–963. [PubMed: 18424607]
261. Kelley DS, Taylor PC, Nelson GJ, Schmidt PC, Mackey BE, Kyle D. Effects of dietary arachidonic acid on human immune response. *Lipids*. 1997; 32(4):449–456. [PubMed: 9113635]
262. Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA*. 2006; 296(15):1885–1899. [PubMed: 17047219]
263. Caughey GE, Mantzioris E, Gibson RA, Cleland LG, James MJ. The effect on human tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$  production of diets enriched in *n*-3 fatty acids from vegetable oil or fish oil. *Am J Clin Nutr*. 1996; 63(1):116–122. [PubMed: 8604658]
264. Endres S, Ghorbani R, Kelley VE, et al. The effect of dietary supplementation with *n*-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *N Engl J Med*. 1989; 320(5):265–271. [PubMed: 2783477]
265. Meydani SN, Endres S, Woods MM, et al. Oral (*n*-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation: comparison between young and older women. *J Nutr*. 1991; 121(4):547–555. [PubMed: 2007907]
266. Lopez-Garcia E, Schulze MB, Manson JE, et al. Consumption of (*n*-3) fatty acids is related to plasma biomarkers of inflammation and endothelial activation in women. *J Nutr*. 2004; 134(7):1806–1811. [PubMed: 15226473]
267. Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Willett WC, Rimm EB. Habitual dietary intake of *n*-3 and *n*-6 fatty acids in relation to inflammatory markers among US men and women. *Circulation*. 2003; 108(2):155–160. [PubMed: 12821543]
268. Ferrucci L, Cherubini A, Bandinelli S, et al. Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. *J Clin Endocrinol Metab*. 2006; 91(2):439–446. [PubMed: 16234304]
269. Micallef MA, Munro IA, Garg ML. An inverse relationship between plasma *n*-3 fatty acids and C-reactive protein in healthy individuals. *Eur J Clin Nutr*. 2009; 63(9):1154–1156. [PubMed: 19352379]
270. Farzaneh-Far R, Harris WS, Garg S, Na B, Whooley MA. Inverse association of erythrocyte *n*-3 fatty acid levels with inflammatory biomarkers in patients with stable coronary artery disease: The Heart and Soul Study. *Atherosclerosis*. 2009; 205(2):538–543. [PubMed: 19185299]
271. Tartibian B, Maleki BH, Abbasi A. Omega-3 fatty acids supplementation attenuates inflammatory markers after eccentric exercise in untrained men. *Clin J Sport Med*. 2011; 21(2):131–137. [PubMed: 21358504]
272. Ranjekar PK, Hinge A, Hegde MV, et al. Decreased antioxidant enzymes and membrane essential polyunsaturated fatty acids in schizophrenic and bipolar mood disorder patients. *Psychiatry Res*. 2003; 121(2):109–122. [PubMed: 14656446]
273. Hibbeln JR. Fish consumption and major depression. *Lancet*. 1998; 351(9110):1213. [PubMed: 9643729]
274. Hibbeln JR. Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *J Affect Disord*. 2002; 69(1–3):15–29. [PubMed: 12103448]
275. Noaghiul S, Hibbeln JR. Cross-national comparisons of seafood consumption and rates of bipolar disorders. *Am J Psychiatry*. 2003; 160(12):2222–2227. [PubMed: 14638594]
276. Peet M. International variations in the outcome of schizophrenia and the prevalence of depression in relation to national dietary practices: an ecological analysis. *Br J Psychiatry*. 2004; 184:404–408. [PubMed: 15123503]

277. Appleton KM, Rogers PJ, Ness AR. Updated systematic review and meta-analysis of the effects of *n*-3 long-chain polyunsaturated fatty acids on depressed mood. *Am J Clin Nutr.* 2010; 91(3): 757–770. [PubMed: 20130098]
278. Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry.* 2006; 67(12):1954–1967. [PubMed: 17194275]
279. Lin PY, Su KP. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. *J Clin Psychiatry.* 2007; 68(7):1056–1061. [PubMed: 17685742]
280. Stoffel W, Holz B, Jenke B, et al.  $\Delta$ 6-desaturase (*FADS2*) deficiency unveils the role of omega-3- and omega-6-polyunsaturated fatty acids. *EMBO J.* 2008; 27(17):2281–2292. [PubMed: 19172737]
281. Obukowicz MG, Welsch DJ, Salsgiver WJ, et al. Novel, selective  $\Delta$ 6 or  $\Delta$ 5 fatty acid desaturase inhibitors as anti-inflammatory agents in mice. *J Pharmacol Exp Ther.* 1998; 287(1):157–166. [PubMed: 9765335]
282. Merino DM, Ma DW, Mutch DM. Genetic variation in lipid desaturases and its impact on the development of human disease. *Lipids Health Dis.* 2010; 9:63. [PubMed: 20565855]
283. Do HJ, Chung HK, Moon J, Shin MJ. Relationship between the estimates of desaturase activities and cardiometabolic phenotypes in Koreans. *J Clin Biochem Nutr.* 2011; 49(2):131–135. [PubMed: 21980230]
284. Martinelli N, Girelli D, Malerba G, et al. *FADS* genotypes and desaturase activity estimated by the ratio of arachidonic acid to linoleic acid are associated with inflammation and coronary artery disease. *Am J Clin Nutr.* 2008; 88(4):941–949. [PubMed: 18842780]
285. Standl M, Sausenthaler S, Lattka E, et al. GINIplus and LISApplus Study Group. *FADS* gene variants modulate the effect of dietary fatty acid intake on allergic diseases in children. *Clin Exp Allergy.* 2011; 41(12):1757–1766. [PubMed: 21793953]
286. Yu G, Björkstén B. Polyunsaturated fatty acids in school children in relation to allergy and serum IgE levels. *Pediatr Allergy Immunol.* 1998; 9(3):133–138. [PubMed: 9814727]
287. Malerba G, Schaeffer L, Xumerle L, et al. SNPs of the *FADS* gene cluster are associated with polyunsaturated fatty acids in a cohort of patients with cardiovascular disease. *Lipids.* 2008; 43(4):289–299. [PubMed: 18320251]
288. Marquardt A, Stöhr H, White K, Weber BH. cDNA cloning, genomic structure, and chromosomal localization of three members of the human fatty acid desaturase family. *Genomics.* 2000; 66(2): 175–183. [PubMed: 10860662]
289. Tanaka T, Shen J, Abecasis GR, et al. Genome-wide association study of plasma polyunsaturated fatty acids in the InCHIANTI study. *PLoS Genet.* 2009; 5(1):e1000338. [PubMed: 19148276]
290. Stafford AN, Rider SH, Hopkin JM, Cookson WO, Monaco AP. A 2.8 Mb YAC contig in 11q12-q13 localizes candidate genes for atopy: Fc epsilon RI  $\beta$  and CD20. *Hum Mol Genet.* 1994; 3(5): 779–785. [PubMed: 7521709]
291. Chapman K, Mustafa Z, Irvén C, et al. Osteoarthritis-susceptibility locus on chromosome 11q, detected by linkage. *Am J Hum Genet.* 1999; 65(1):167–174. [PubMed: 10364529]
292. Daniels SE, Bhattacharya S, James A, et al. A genome-wide search for quantitative trait loci underlying asthma. *Nature.* 1996; 383(6597):247–250. [PubMed: 8805698]
293. Palmer LJ, Daniels SE, Rye PJ, et al. Linkage of chromosome 5q and 11q gene markers to asthma-associated quantitative traits in Australian children. *Am J Respir Crit Care Med.* 1998; 158(6):1825–1830. [PubMed: 9847274]
294. Aulchenko YS, Ripatti S, Lindqvist I, et al. ENGAGE Consortium. Loci influencing lipid levels and coronary heart disease risk in 16 European population cohorts. *Nat Genet.* 2009; 41(1):47–55. [PubMed: 19060911]
295. Fallin MD, Lasseter VK, Wolynec PS, et al. Genome-wide linkage scan for bipolar-disorder susceptibility loci among Ashkenazi Jewish families. *Am J Hum Genet.* 2004; 75(2):204–219. [PubMed: 15208783]
296. Liu Y, McNamara RK. Elevated  $\Delta$ 6-desaturase (*FADS2*) gene expression in the prefrontal cortex of patients with bipolar disorder. *J Psychiatr Res.* 2011; 45(2):269–272. [PubMed: 20615514]

297. Barbosa NR, Junqueira RM, Vallada HP, Gattaz WF. Association between BanI genotype and increased phospholipase A2 activity in schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 2007; 257(6):340–343. [PubMed: 17629734]
298. Dikeos DG, Papadimitriou GN, Souery D, et al. Lack of genetic association between the phospholipase A2 gene and bipolar mood disorder in a European multicentre case–control study. *Psychiatr Genet*. 2006; 16(4):169–171. [PubMed: 16829784]
299. Meira-Lima I, Jardim D, Junqueira R, Ikenaga E, Vallada H. Allelic association study between phospholipase A2 genes and bipolar affective disorder. *Bipolar Disord*. 2003; 5(4):295–299. [PubMed: 12895207]
300. Pae CU, Yu HS, Kim JJ, et al. BanI polymorphism of the cytosolic phospholipase A2 gene and mood disorders in the Korean population. *Neuropsychobiology*. 2004; 49(4):185–188. [PubMed: 15118355]
301. Su KP, Huang SY, Peng CY, et al. Phospholipase A2 and cyclooxygenase-2 genes influence the risk of interferon- $\alpha$ -induced depression by regulating polyunsaturated fatty acids levels. *Biol Psychiatry*. 2010; 67(6):550–557. [PubMed: 20034614]
302. Papiol S, Rosa A, Gutiérrez B, et al. Interleukin-1 cluster is associated with genetic risk for schizophrenia and bipolar disorder. *J Med Genet*. 2004; 41(3):219–223. [PubMed: 14985387]
303. Czernski PM, Rybakowski F, Kapelski P, et al. Association of tumor necrosis factor-308G/A promoter polymorphism with schizophrenia and bipolar affective disorder in a Polish population. *Neuropsychobiology*. 2008; 57(1–2):88–94. [PubMed: 18515978]
304. Pae CU, Lee KU, Han H, Serretti A, Jun TY. Tumor necrosis factor- $\alpha$  gene-G308A polymorphism associated with bipolar I disorder in the Korean population. *Psychiatry Res*. 2004; 125(1):65–68. [PubMed: 14967554]
305. Meira-Lima IV, Pereira AC, Mota GF, et al. Analysis of a polymorphism in the promoter region of the tumor necrosis factor- $\alpha$  gene in schizophrenia and bipolar disorder: further support for an association with schizophrenia. *Mol Psychiatry*. 2003; 8(8):718–720. [PubMed: 12888800]
306. Amminger GP, Schäfer MR, Papageorgiou K, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. *Arch Gen Psychiatry*. 2010; 67(2):146–154. [PubMed: 20124114]
307. Nemets H, Nemets B, Apter A, Bracha Z, Belmaker RH. Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. *Am J Psychiatry*. 2006; 163(6):1098–1100. [PubMed: 16741212]
308. Soczynska JK, Kennedy SH, Goldstein BI, Lachowski A, Woldeyohannes HO, McIntyre RS. The effect of tumor necrosis factor antagonists on mood and mental health-associated quality of life: novel hypothesis-driven treatments for bipolar depression? *Neurotoxicology*. 2009; 30(4):497–521. [PubMed: 19477018]
309. Kekow J, Moots R, Khandker R, Melin J, Freundlich B, Singh A. Improvements in patient-reported outcomes, symptoms of depression and anxiety, and their association with clinical remission among patients with moderate-to-severe active early rheumatoid arthritis. *Rheumatology (Oxford)*. 2011; 50(2):401–409. [PubMed: 21059675]
310. Tying S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised Phase III trial. *Lancet*. 2006; 367(9504):29–35. [PubMed: 16399150]
311. Stolk P, Souverein PC, Leufkens HG, Weil JG, Egberts AC, Heerdink ER. The association between exposure to COX-2 inhibitors and schizophrenia deterioration. A nested case–control study. *Pharmacopsychiatry*. 2007; 40(3):111–115. [PubMed: 17541886]
312. Elisa B, Beny L. Induction of manic switch by the tumour necrosis factor- $\alpha$  antagonist infliximab. *Psychiatry Clin Neurosci*. 2010; 64(4):442–443. [PubMed: 20653912]
313. Esposito G, Giovacchini G, Liow JS, et al. Imaging neuroinflammation in Alzheimer’s disease with radiolabeled arachidonic acid and PET. *J Nucl Med*. 2008; 49(9):1414–1421. [PubMed: 18703605]

### Key issues

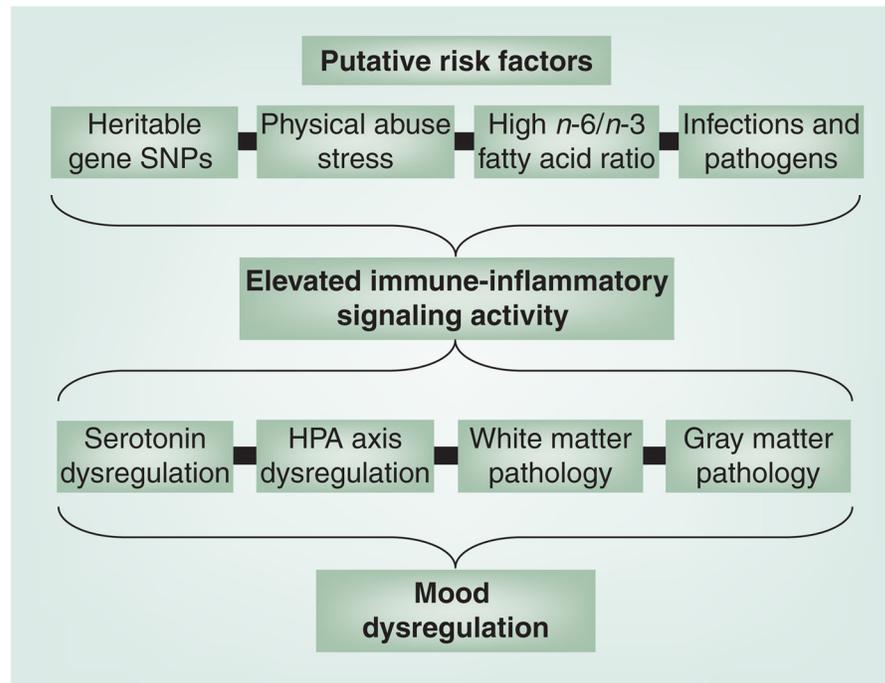
- Convergent translational evidence has implicated elevated immune-inflammatory signaling in the pathophysiology of mood disorders.
- Both genetic and environmental factors including diet may contribute to elevated immune-inflammatory signaling in mood disorders.
- Emerging data suggest that medications 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  $\Delta$ 6-desaturase. Phospholipid-bound AA is mobilized by cPLA<sub>2</sub>, and free AA may be metabolized by COX-1 and -2 enzymes to produce PGH<sub>2</sub> and PGE<sub>2</sub>. PGE<sub>2</sub> stimulates the biosynthesis of IL-6, and proinflammatory cytokines including IL-1 $\beta$ , IL-6 and TNF- $\alpha$  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.,  $\alpha$ -linolenic acid), which competes with and decrease  $\Delta$ 6-desaturase-mediated LA $\rightarrow$ AA biosynthesis. Mood-stabilizer and atypical antipsychotic medications, as well as LC*n*-3 fatty acids, decrease PLA<sub>2</sub>-mediated AA mobilization from phospholipids, and aspirin and celecoxib decrease COX-mediated PGE<sub>2</sub> biosynthesis. Different antidepressant medications have been found to augment PLA<sub>2</sub>-mediated AA turnover, without altering COX enzyme activity or PGE<sub>2</sub> production, and to downregulate serotonin metabolism (5-HIAA).

5-HIAA: 5-Hydroxyindoleacetic acid; AA: Arachidonic acid; COX: Cyclooxygenase; cPLA<sub>2</sub>: Calcium-dependant phospholipase A<sub>2</sub>; 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.