Total Word Count: 16,194

Word Count excluding abstract, tables, figures and references: 7,808

Abstract: 236

Tables: 1,661

THE ROLE OF CYTOKINES IN DEPRESSION IN ADOLESCENTS: A SYSTEMATIC REVIEW

Natalie T Mills[1], James G Scott[2,3], Naomi R Wray [4], Sarah Cohen-Woods[5,] Bernhard T Baune[5]

[1] *Genetic Epidemiology, Queensland Institute of Medical Research, Brisbane, QLD, Australia*

[2] *The University of Queensland Centre for Clinical Research, Brisbane, Australia*

[3] *Metro North Mental Health, RBWH, Brisbane, Australia*

[4] *Queensland Brain Institute, University of Queensland, Brisbane, Australia*

[5]*Discipline of Psychiatry, School of Medicine, University of Adelaide, Adelaide, SA, Australia*

Running Head: Inflammation in Adolescence

* Address for Correspondence

Bernhard T. Baune, PhD, MD, MPH, FRANZCP

Professor and Chair of Psychiatry

Discipline of Psychiatry; School of Medicine; University of Adelaide; Adelaide, SA 5005

AUSTRALIA

Ph: +61 8 8222 5141; Fax: +61 8 8222 2865; Email: Bernhard.Baune@Adelaide.edu.au

Abstract

Background: Cytokines have been implicated in the pathophysiology of depression in adults, however the potential role in younger age groups such as adolescents is less clear. We review the literature (i) exploring the relationship between cytokines and depression in adolescents and (ii) examining how cytokines may be related to adolescent depression in the context of other neurobiological theories of depression.

Method: A systematic review of the scientific literature on the subject was conducted in February 2013, searching the Web of Knowledge, PubMed (Medline), PsycInfo, and Cochrane electronic databases.

Results: Eighteen studies were identified measuring both depression or depressive symptoms and cytokines or immune markers in adolescents. Adolescents with depression show age specific characteristics of the immune and inflammatory system, specifically in NK cell activity and in pro-inflammatory cytokines (such as IL-1β and TNF-α). In addition, the role of cytokines in adolescent depression is influenced by neurodevelopment, hormonal changes, stress, and trauma.

Conclusions: There may be differences in the neurobiology of adolescent MDD compared to adult MDD. Increased understanding of the role of cytokines in adolescent MDD may lead to improved outcomes in the treatment of adolescent depression.

Key Words: Cytokines, inflammation, immune system, adolescents, depression, cognition, stress

Abbreviations: MDD=Major Depressive Disorder; CD=Conduct Disorder; HPA=Hypothalamic-Pituitary-Adrenal; IL=interleukin; TNF-α=tumor necrosis factor-α; IFN-γ=interferon-γ; NK cells =natural killer cells; TRP=tryptophan; KYN=kynurenine; 3-HAA=3-hydroxyanthranilic acid; QUIN=quinolinic acid; tCho=total choline; PUFAs=polyunsaturated fatty acids; CRH= corticotrophin-releasing hormone; CRP=C-reactive protein; LPS=lipopolysaccharide; SSRI=selective serotonin re-uptake inhibitor

Conflict of Interest:

All authors declare no conflict of interest.

Introduction

Major depression is a leading cause of disability worldwide (Moussavi et al., 2007), with lifetime prevalence in most countries ranging between 8 to 12% (Andrade et al., 2003). It is responsible for the greatest proportion of disease burden attributable to non-fatal health outcomes, accounting for almost 12% of total years lived with disability worldwide (Ustun and Chatterji, 2001). Major Depressive Disorder (MDD) in young people is estimated to be experienced by approximately 2% of children and 4% to 8% of adolescents (Birmaher et al., 1996) and carries its own burden of disadvantage often persisting or reemerging in adulthood (Weissman et al., 1999, Dunn and Goodyer, 2006). The Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM IV) considers major depression in adolescents and adults to be similar, although adolescents may show irritability rather than report depressed mood (APA, 2000). The 5th edition of the DSM (DSM 5) maintains these criteria (APA, 2011). Similarities in the clinical presentation of MDD in children, adolescents and adults are supported by additional evidence (e.g. (Kovacs, 1996, Kaufman et al., 2001)), yet there is also support for differences in risk factors, clinical outcome, and biological correlates between adults and adolescents (Zisook et al., 2004, McDermott et al., 2010, Kaufman et al., 2001, Hill et al., 2004, Jaffee et al., 2002). Apparent differences in underlying aetiologies between adolescent- and adult- onset depression (Kaufman et al., 2001) may be attributable to developmental differences, or biologic changes that are sub-syndromal and too subtle for studies designed to detect the effect sizes reported in adult studies. Alternatively, it could be speculated that biologic changes observed in depressed adults but not in adolescents or children might be attributable to medication intake

since adults with depression often have a prolonged medication history as compared to adolescents and children with depression.

Although there are differences in risk factors for depression in adolescent- and adult-onset depression, family history and stressful life events including childhood maltreatment are significant risk factors for both (Goodyer, 2008, Jaffee et al., 2002). A family history of depression does not automatically indicate a genetic contribution to the disorder, as it reflects both shared genetic and common (family) environmental effects. However, twin studies designed to tease out the heritability (proportion of variance that can be attributed to genetic factors), consistently indicate a substantial genetic component, particularly in clinical samples (e.g. (McGuffin et al., 1996)). Yet, identification of gene variants that robustly associated with depression have remained elusive, with environmental factors that interact with genetic predisposition being of potential relevance. A particularly important environmental mediator in depression is stressful life events, particularly childhood maltreatment (Nanni and Valentina, 2012). Such experience may result in dysregulation of the adaptive stress response system (Danese et al., 2007). To investigate the interaction of genetic and environmental risk factors requires large data sets in which participants have provided DNA and have been consistently measured, preferably longitudinally, for environmental risk factors. Unfortunately, such data sets are rare. The on-going debate about the interaction between stressful life events and the serotonin transporter length polymorphism illustrates how differences in the measurement of environmental risk factors might, in part, be responsible for inconsistent findings between studies (Caspi et al., 2003, Risch et al., 2009, Karg et al., 2011, Uher et al., 2011, McGuffin et al., 2011).

In adults, accumulating evidence suggests that MDD may be associated with immune system dysregulation (Irwin and Miller, 2007), at times occurring in the absence of specific immune challenges such as infections. Cytokines are signaling molecules that mediate key steps in cellular and humoral immunity, and a biological relationship with MDD is supported by a large number of mechanistic studies in vivo and in vitro (Dantzer et al., 2008). Cytokine genes, such as variants of the *IL-1β* and *TNF-α* genes, have been implicated in impaired emotion processing in major depression and in hippocampus formation in recent fMRI studies (Baune et al., 2010, Baune et al., 2012b). Furthermore, a recent review suggested that genetic variants of cytokines are possibly involved in the pathophysiology of depression (Bufalino et al., 2012). Of particular relevance, cytokines have also been implicated in the stress response, important in depression (Szelenyi and Vizi, 2007). In both adults and adolescents, childhood maltreatment has been associated with an elevation in CRP levels, indicating a dysregulation of the immune system, further compounded by concurrent depressive symptoms (Danese et al., 2011, Danese et al., 2007). In addition, cytokines are implicated in neurodevelopment and with stress regulation since pro-inflammatory cytokines may exert direct effects on the hypothalamic-pituitary-adrenal (HPA) axis (Janssen et al., 2010, Song, 2002). Prolonged periods of excess corticosteroids following chronic stress are particularly important during adolescence, as brain structures such as the hippocampus are susceptible to adverse stress-associated effects (McKittrick et al., 2000). Also, biological susceptibility to stress related brain damage may be heightened during adolescence when myelination processes within the central corticolimbic circuitry of the brain occur (Benes, 1989).

The primary purpose of this review is to assess literature on the role of cytokines in adolescent depression by identifying studies that measured both cytokines and symptoms of depression in adolescents. By doing this, we aim to clarify if cytokines have a differential role in depression in adolescents compared to adults. The secondary purpose of this review is to examine how cytokines may be related to adolescent depression in the context of other neurobiological theories of depression.

Method

The literature search included published articles until February 2013 according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines as they apply to systematic reviews (Liberati et al., 2009). The primary purpose was to identify all studies that provide empirical data on the measurement of cytokines and symptoms of depression in adolescents. In order to compare findings in adolescents to other age groups, the search was expanded to all age groups. In addition, as some studies in older patients with MDD found a relationship between cytokines and cognition and cognitive dysfunction which may present as a symptom in depression, we also searched for studies that measured cytokines and cognitive performance in adolescents. As a family history of depression is also considered a risk for MDD, 'genes' was included as a search term. To help identify publications considering a differential role for cytokines and immune markers in adolescent MDD, we conducted a further literature search applying the following combination of search terms – Cytokines, Immun*, and Depression and Stress. The final search strategy is illustrated in Figure 1.

[Insert Figure 1 about here]

Results

Several detailed reviews have reported on the cytokine theory of depression (Haroon et al., 2011, Capuron and Miller, 2011, Dowlati et al., 2010, Janssen et al., 2010, Maes et al., 2009, Dantzer, 2009, Dantzer et al., 2008, Miller et al., 2009, Loftis et al., 2010, Sharpley and Agnew, 2011), with a primary focus on adults, or older age groups. Our review comprises three main sections: (i) the cytokine theory of depression as reported in adults, (ii) evidence specifically relevant to adolescent-onset depression, and (iii) clinical implications.

I.   The Cytokine Theory of Depression

Biological Properties of Cytokines

Cytokines are small pleiotropic proteins (Khairova et al., 2009). The term cytokine includes a large and diverse family of signaling molecules that primarily have immune modulating activity, and are produced widely throughout the body by cells of diverse embryological origin (Ransahoff and Benveniste, 2006, Rothwell and Loddick, 2002). Cytokines can be viewed as either 'pro-inflammatory' or 'anti-inflammatory', depending on their primary effects on target cells (Khairova et al., 2009). Pro-inflammatory cytokines include interleukin-1α and β (IL-1α and IL-1β), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). These molecules are believed to co-ordinate the local and systemic inflammatory response to microbial pathogens (Dantzer et al., 2008). Others, such as interleukin 10 (IL-10), are

considered 'anti-inflammatory'(Rothermundt et al., 2001), however this distinction of pro and anti-inflammatory cytokines has been regarded as an over-simplification in the context of depression (Janssen et al., 2010). In the brain, as in systemic organs, the natural balance between pro- and anti-inflammatory cytokines regulates the intensity and duration of the response to immune stimuli (Dantzer et al., 2008).

Heritability of cytokine levels (IL-1β, IL-1ra, IL-6, IL-10, and TNF-α) have been estimated to exceed 50% (De Craen et al., 2005). However, in this study cytokine levels were measured with an ex-vivo whole blood assay in response to lipopolysaccharide (LPS) stimulation, so heritability estimates may more accurately reflect "immune-response" and not necessarily naturally circulating levels of cytokines in the blood. Nonetheless, other studies based on circulating levels of cytokines implicate an important role for genetic factors (e.g.(Worns et al., 2006, Sas et al., 2012, Raggi et al., 2010)). Dysfunction in genes controlling key proteins in cytokine production have been identified as vulnerability factors for cytokine-induced depression (Dantzer, 2009), and recent studies have reported that variation in *IL-1* and *TNF-α* genes, and elevated levels of *TNF-α*, are associated with reduced responsiveness to antidepressant treatment (Jun et al., 2003, Rosa et al., 2004, Fertuzinhos et al., 2004). Overall, the molecular genetic basis of cytokine production in humans in the context of depression is currently not well understood.

Cytokines and Depression

Increasing evidence suggests that pro-inflammatory cytokines play a major role in the pathophysiology of depression. A role of cytokines in depression was first proposed by Smith in

the form of the 'macrophage theory of depression' stating that excessive secretion of macrophage monokines cause depression (Smith, 1991). Although no consistent association between cytokines and MDD has been reported (Einvik et al., 2012, Steptoe, 2003), a recent meta-analysis that included 24 studies reported an association between elevated levels of two pro-inflammatory cytokines, IL-6 and TNF-α, and major depression (Dowlati et al., 2010).

Additional research in humans is required to clarify whether cytokines are causally involved in clinical depression since the majority of studies have been cross-sectional (Sharpley and Agnew, 2011), with only a few prospective studies in humans allowing for causal inferences. For example, findings from a 12 year study of a large British occupational cohort in adults concluded that inflammation predicted cognitive symptoms of depression (Gimeno et al., 2009). Moreover, in support of a role of inflammation in the etiology of depression, Baune et al. showed in older adults that the pro-inflammatory cytokine IL-8 predicted first onset of mild to moderate depressive symptoms over a 2 year period, indicating IL-8 could be a marker of first onset of depressive symptoms in the elderly (Baune et al., 2012c). Such studies are sparse in adolescents with clinical depression, and would require a longitudinal study design.

A direct involvement of cytokines in clinical depression is supported by the view that interactions between biological factors and environmental conditions are significant in the etiology and pathophysiology of depression. For example, external factors such as psychosocial stressors and medical conditions such as organic inflammatory disorders or physiological conditions (i.e. the postpartum period), may trigger clinical depression via inflammatory processes (Maes et al., 2009). Clinical depression may also be induced by a therapeutic administration of interferon in hepatitis C (Udina et al., 2012). Experimentally, peripheral

administration of lipopolysaccharide (LPS), or of recombinant cytokines, such as IL-1β or TNF-α, induces nonspecific symptoms of sickness, including fever, activation of the HPA axis, reduction of food intake, and withdrawal from the physical and social environment, termed as *sickness behaviour* (Dantzer, 2009).

Further mechanistic studies demonstrate that LPS not only causes a peripheral inflammatory response, but also induces a neuroinflammatory reaction with increased production of pro-inflammatory cytokines such as TNF-α in the brain (Qin et al., 2007, Kent et al., 1992). Pre-treatment with antidepressant drugs have also been found to abrogate LPS- or IL-1β- behaviour related to reduced consumption or rewards of sweetened solutions or sucrose in rats (Merali et al., 2003, Yirmiya et al., 1999). Although brain circuits involved in depression-like behavior have been identified using LPS induction of cytokines in animal models (e.g., amygdala, hippocampus, hypothalamus), a functional dissociation between those brain structures that underlie cytokine-induced sickness behavior and cytokine-induced depressive-like behavior has been reported, indicating the need for further research on the temporal relationship between cytokine elevation, structural and behavioural changes (Frenois et al., 2007). Figure 2 shows the cellular and humoral immune factors implicated to have a role in depression. Specifically, cellular neuroimmune mechanisms implicated in the pathophysiology of depression include dysfunction of T helper (Th 17) cells and CD4+CD25+ T regulatory (Treg) cells (Capuron and Miller, 2011, Eyre and Baune, 2011). Findings on the possible involvement of natural killer (NK) cells in adult and adolescent MDD are discussed later.

[Insert figure 2 about here]

11

Cytokines in the brain

Cytokines can exert direct and indirect effects on brain function through their influence on neurotransmitters, neurogenesis, and the HPA axis influencing neuroplastic changes relevant to depression (Eyre and Baune, 2012). While cytokines do not readily pass through the blood-brain barrier (Haroon et al., 2011), five potential pathways for cytokine signals to reach the brain have been described: 1) passive transport of cytokines into the brain at circumventricular sites lacking a blood-brain barrier (Ericsson et al., 1994, Komaki et al., 1992, Breder et al., 1988); 2) activation of the cerebral vascular endothelium, thereby releasing cytokines and inducing the generation of secondary messengers such as prostaglandins and nitric oxide (Cao et al., 1997, Fabry et al., 1993, Kilbourn and Belloni, 1990); 3) carrier-mediated transport of cytokines into the brain across the blood-brain barrier (Banks et al., 1989); 4) activation by cytokines of peripheral afferent nerve terminals, which then relay cytokine signals to relevant brain regions (Watkins et al., 1994, Ericsson et al., 1994, Bluthe et al., 1994); and 5) recruitment of activated cells such as monocytes / macrophages from the periphery to the brain, where these cells can produce cytokines (D'Mello et al., 2009). These mechanisms are not mutually exclusive, and depend in part on the location of the inflammatory stimulus and the disease state of the organism (Kronfol and Remick, 2000). In addition, most cytokines can be synthesized and released within the CNS (Kronfol and Remick, 2000) such as by microglia that are a primary source of pro-inflammatory cytokine production in the brain (Miller et al.,

2009). However, the brain circuitry that mediates the various behavioural responses to cytokines remains elusive (Dantzer et al., 2008).

Clinical and experimental studies indicate that stress and depression are also associated with increased circulating concentrations of cytokines, such as TNF-α and IL-1 (Connor and Leonard, 1998). Increased levels of these cytokines have the potential to impair synaptic plasticity (structurally and functionally), modulate long-term potentiation (LTP) and glutamatergic-dependent synaptic plasticity (Carlezon Jr. and Nestler, 2002, Du et al., 2004, Du et al., 2007, Du et al., 2008, Kendell et al., 2005, Malenka, 2003, Sun et al., 2005, Wolf et al., 2004), and to induce fear learning, thus contributing to progression of a depressive disorder (Khairova et al., 2009). It has also been postulated that antidepressants indirectly modulate synaptic plasticity as a mechanism of antidepressant action, and that selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants may induce changes in TNF-α expression and function in the brain (Khairova et al., 2009).

Cytokines influence on biological pathways of depression

Cytokines affect biological pathways that have been associated with depression, and so the cytokine theory in depression can be viewed as complimentary rather than competitive to other hypotheses of depression, such as the monoamine theory of depression. Tryptophan is an essential amino acid required for protein synthesis and is a precursor for the monoamine serotonin and a lowered availability of plasma L-tryptophan has been associated with depression (Ruhe et al., 2007). Interestingly, decreased levels of L-tryptophan are also correlated with inflammation, indicating that systemic inflammation may contribute to clinical

depression via a decrease in the serotonin precursor L-tryptophan (Maes et al., 1993, Maes et al., 1996, Maes et al., 1990).

As depicted in figure 3, pro-inflammatory cytokines induce IDO (indoleamine 2-3-dioxygenase), an enzyme that mediates the catabolism of tryptophan into kynurenine (KYN) (Babcock and Carlin, 2000). KYN is further metabolized into 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HAA), and quinolinic acid (QUIN), which may induce neuronal damage (Goldstein et al., 2000, Schwarcz et al., 1983). Hence, it is suggestive that increased levels and activity of cytokines may lead to depressive symptoms by inducing a reduction in important neurotransmitters such as serotonin and by stimulating neuronal damage both implicated in clinical depression.

[Insert Figure 3 about here]

As cytokines, among other humoral and cellular immune factors, have the potential to influence systems heavily implicated in depression (Eyre and Baune, 2012), it is a clinically relevant question to determine if a genetic predisposition, or environmental factors that frequently associate with depression, or a combination of both, contribute to the pathophysiology of depression. It has been frequently reported that stress elevates levels of pro-inflammatory cytokines by activating their signaling pathways (Deinzer et al., 2004, Goebel et al., 2000, Madrigal et al., 2002, O'Connor et al., 2003). Moreover, cytokines influence the hypothalamic pituitary axis (HPA)(Capuron et al., 2003) and IL-1, IL-6, TNF-α, and IFN-α may increase corticotrophin-releasing hormone (CRH) release and disrupt the function of the glucocorticoid receptor (reviewed by (Cavanagh and Mathias, 2008)). Indeed, since a hyperactive HPA axis has been reported in a proportion of patients with MDD (Capuron et al.,

2003), it is plausible that such hyperactivity could be a consequence of an elevation in cytokines, attributable to potentially both environmental and genetic moderators. Particularly genetic variants of cytokines have been suggested to be associated with clinical depression as recently reviewed by Bufalino et al. (Bufalino et al., 2012). However, the likely important interaction between these genetic variants and environmental factors such as stress and maltreatment has not been considered yet in original studies.

Other genes of potential relevance are polymorphisms of the glucocorticoid receptor gene (*NR3C1*), involved in the regulation of the HPA axis. While some studies have reported that genetic variants of *NR3C1* influence susceptibility to MDD and depressive symptoms (Szczepankiewicz et al., 2011), three further reports found no association, or associations that failed to withstand correction for multiple testing (van West et al., 2006, Mill et al., 2009). In addition, multiple genome-wide studies have presented no evidence for genome-wide significance (PGC, 2012). Failure to replicate may reflect insufficient power, due to insufficient sample size, heterogeneity of the phenotype of depression, or interaction with unidentified environmental factors. Indeed, evidence for gene-environment interaction has been reported with variation in the *NR3C1* gene and childhood maltreatment (Bet et al., 2008), and altered methylation of the *NR3C1* gene has been associated with stress exposure (Meaney and Szyf, 2005, de Rooij et al., 2012). These findings may lead to the speculation that depression could be a consequence of the effect of elevated cytokine levels in response to a stressor, occurring in the context of an *NR3C1* system that was already dysregulated due to genetic or epigenetic effects earlier.

Recent work on the HPA axis and depression has also been conducted by Solomon et al., who showed a sex difference in the role of forebrain glucocorticoid receptors in regulating HPA axis activity and depression-like behavior in mice (Solomon et al., 2012). Specifically, in mice with selective deletion of glucocorticoid receptors in forebrain cortico-limbic sites (forebrain glucocorticoid receptor knockout mouse – FBGRKO), female mice did not show basal HPA axis dysregulation or exaggerated stress responses. The authors noted that in females, glucocorticoid receptor regulation of HPA axis function and behavior may be from other brain areas than those targeted in the FBGRKO mouse (Solomon et al., 2012).

Another biological pathway associated with depression might be a stress-induced decrease in neurogenesis influenced by cytokines. Pro-inflammatory cytokines, such as IL-1β, have been shown to inhibit cell proliferation and promote cell death in the hippocampus (Koo and Duman, 2008). Furthermore, there is evidence that neurodegeneration and the defects in neurogenesis in depression are caused by inflammatory processes, related to the production of oxidative and nitrosative stress molecules and pro-inflammatory cytokines (Maes et al., 2009). Glutamate has also been implicated in MDD (Palucha and Pilc, 2007, Pittenger et al., 2007), and glutamate neurotoxicity represents a pathway leading to increased apoptosis enhanced by pro-inflammatory cytokines via various pathways: (1) via activation of the kynurenine pathway in microglia and increased production of quinolonic acid and glutamate release; (2) via decreasing glial glutamate transporter activity leading to reduced glutamate removal from the extracellular space; and (3) by inducing long-term activation of microglia to release TNF-α and IL-1 in a positive feedback manner (reviewed in McNally et al 2008) (McNally et al., 2008, Khairova et al., 2009).

In summary, cytokines exert wide-ranging influences on neuronal structure, function, and directly on the stress-response system, as well as in response to stress. Evidence for the role of cytokines in the brain in depression is building, and seems tantalizing, yet remains largely circumstantial. Still needed is to clarify whether effects are causal in humans, to better specify the actual molecular mechanisms operating in human depression related to cytokines, and in particular to clarify the effects in adolescence.

II.   The Role of Cytokines in Depression in Adolescents

Emerging literature has examined a possible role of cytokines in adolescent depression. A total of twenty-four articles examining the role of immune markers in depression in adolescents were identified for this review. Of these, eighteen studies report empirical data as summarized in Tables 1, 2, and 3. Twelve publications present case-control studies which have relatively small sample sizes; the largest study consisted of 134 cases and 149 controls. Four studies used a prospective design (Miller and Chen, 2010, Caserta et al., 2011, Miller and Cole, 2012, Copeland et al., 2012), assessing N=135, N=141, N=147, and N=1420 individuals respectively for depressive symptoms. The two remaining studies are a cross-sectional representative community sample (Chaiton et al., 2010), and an observational study of youths with diabetes (Hood et al., 2012). Key results from the studies are included in the relevant sections below. Of the remaining 6 articles examining the role of immune markers in depression in adolescents, some did not measure cytokines (for example cytokine genes were genotyped but not circulating cytokine levels (Misener et al., 2008); Pandey et al. measured serotonin receptors postmortem and discussed the interaction between the HPA axis and

serotonergic system (Pandey et al., 2002)). Two of these remaining 6 articles measured inflammatory markers or cytokines only when the cohort had reached adulthood (Danese et al., 2008, Danese et al., 2007). Of these 6 articles, the studies by Danese et al. 2007, Danese et al. 2008, and Pandey et al. 2002 are discussed in more detail later in the review.

Stress Response, Neurogenesis and Neurodevelopment

Increased levels of pro-inflammatory cytokines in response to acute stress has been described as characteristic (Eyre and Baune, 2011), involving an activated HPA axis that may lead to a further rise in pro-inflammatory cytokines through complex positive feedback loops (Janssen et al., 2010). These mechanisms could be particularly important during adolescence, as brain structures such as the hippocampus appear susceptible to adverse effects of prolonged periods of excess corticosteroids with consequences such as atrophy of the apical dendrites of the pyramidal cells (McKittrick et al., 2000). Therefore, chronic unpredictable stress in the environment is regarded as an important factor in the development and onset of depression (Eyre and Baune, 2011).

The variation in how an individual responds to stress, including their vulnerability to depression, may be influenced by an inflammatory response of the immune system. In a recent review, Fagundes et al. proposed a model of early adversity leading to greater stress sensitivity, and so placing an individual at greater risk for immune dysregulation (Fagundes et al., 2013). Elevated levels of inflammatory markers, specifically C-reactive protein (CRP), have been reported not only in depressed adults exposed to childhood maltreatment (Taylor et al., 2006, Danese et al., 2007, Danese et al., 2011), but also in adolescence (Danese et al., 2011). CRP is

an acute phase protein that promotes resistance to infection and repair of damaged tissues (Danese et al., 2007). In these studies, CRP levels showed a linear increase depending on depression and/or maltreatment exposure (Danese et al., 2011, Danese et al., 2008). Individuals with a history of depression or current depression exhibited higher CRP levels relative to individuals with no depression or exposure to maltreatment; those with a history of maltreatment and no depression exhibited even higher levels of CRP, and finally those that had experienced both maltreatment and depression presented the most elevated profile of all the groups. The elevation in CRP levels was significant in the combined depressed and maltreated group, relative to those with no exposure to maltreatment or depression. The authors concluded that a history of childhood maltreatment has a significant role in explaining the co-occurrence of depression and inflammation through the lifespan with "biological embedding" already seen at adolescence (Danese et al., 2011, Danese et al., 2008). The findings in adolescents (Danese et al 2011) are particularly important, as increased inflammatory markers in adulthood has been linked to increased risk of both mental and physical illness (Danese et al., 2008, Miller et al., 2009).

In adolescents, pro-inflammatory cytokines have also been implicated in the stress response with a higher number of stressful life events associated with higher TNF-α levels (Dixon et al., 2009). In support of these findings is an 18-month longitudinal study of adolescent females who showed increased IL-6 responses to two different types of threatening stimuli on the background of exposure to a harsh family environment (Miller and Chen, 2010). An extension of this study that investigated circulating levels of IL-6 and CRP found that among those exposed to higher levels of childhood adversity, the transition to depression was also

accompanied by relative increases in both CRP and IL-6 (Miller and Cole, 2012). Furthermore, the authors noted that higher CRP levels remained in these subjects 6 months later, even after the episode of depression had abated. Importantly, this coupling of depression and inflammation was not apparent in those without a history of childhood adversity (Miller and Cole, 2012).

Cytokines also appear to be involved in neurodevelopmental processes (Wilson et al., 2002); for example, IL-6 has demonstrated both neuroprotective (Peng et al., 2005, Godbout and Johnson, 2004) and neurodegenerative properties (Morales et al., 2010). In support of a possible neuroprotective effect of IL-6 is a recently published neuroimaging study conducted in healthy individuals that showed increased hippocampus volumes associated with genetic variants of the *IL-6* gene (Baune et al., 2012a). There is also some preliminary evidence suggesting that maternal psychopathology and HPA function influences fetal, infant, and adolescent HPA axis function resulting in a higher tonic setting of the HPA axis through epigenetic programming (Talge et al., 2007, Weaver et al., 2004). Psychiatric epigenetics is a relatively new field, however it does provide a biological mechanism by which stress might influence the immune response, and ultimately predispose to depression. Moreover, such mechanisms could lead to atypical early neurogenesis and vulnerable neural systems in the post-pubertal adolescent brain (Goodyer, 2008). Such a sensitization of the neurobiological systems implicated in stress adaptation and response (as is seen in childhood maltreatment) may increase the risk of developing depression (McCrory et al., 2010). Therefore, as individuals move through different stages of adolescence, the risk for depression as a consequence of stress exposure may change, and arguably so might the inflammatory stress-response profile.

To date little gene-environment work has focused on stress exposure and depression onset in adolescents specifically – the stress exposure has primarily focused on either adulthood or childhood (although this at times spans adolescent years) (e.g. (Fisher et al., 2012, Caspi et al., 2003).

Cytokines and onset of Depression during Adolescence

Similarly to adult MDD, immune system dysregulation with a pro- and anti-inflammatory imbalance has been proposed in MDD in adolescents (Gabbay et al., 2009a). The first study to examine cytokines in adolescent MDD, reported increased pro-inflammatory cytokines IFN-γ and IFN-γ/IL-4 as well as a trend for increased IL-6 in adolescents with MDD compared to healthy controls (Gabbay et al., 2009a).

In an attempt to examine the neurobiology of clinical subtypes of depression in adolescence, Gabbay et al. examined whether adolescent MDD with melancholic features (M-MDD) has distinct biological features in the kynurenine pathway. As previously reported, pro-inflammatory cytokines induce IDO, which metabolizes tryptophan (TRP) into kynurenine (KYN), eventually decreasing TRP availability in the brain (Gabbay et al., 2010). The authors reported decreased plasma TRP levels and an increased KYN/TRP ratio (estimating IDO activity) in adolescents with M-MDD compared to both non M-MDD and a control group. Interestingly, the severity of episodes as measured by Children's Depression Rating Scale-Revised (CDRS-R) was associated with several KYN pathway measures (e.g., KYN and 3-hydroxyanthranilic acid (3-HAA)/KYN) in the M-MDD group (Gabbay et al., 2010).

Investigating the relationship between early onset of depression and anxiety, IL-10 levels have been associated with increased anxiety and depression scores, and IFNα2 levels with anxiety scores only (Quinones et al., 2012). The association between IFNα2 levels and anxiety scores remained significant after controlling for familial risk of MDD, gender, current stress, and childhood trauma (Quinones et al., 2012), suggesting an independent effect of cytokines in anxiety.

Of clinical relevance is the potential that cytokine levels are modified during treatment with antidepressants (Janssen et al., 2010). In a clinical sample of adolescent females with MDD and/or anxiety disorder the effects of antidepressant treatment with SSRIs on cytokine levels was compared to healthy controls (Henje Blom et al., 2011). The overall sample showed significantly increased levels for IL-1β, IL-2 and IL-10 as compared to healthy controls , with SSRI-treatment associated with IL-6 levels in the clinical sample (Henje Blom et al., 2011). The non-SSRI subgroup showed significantly higher levels of IL-1β, IL-2, and IL-6 compared to healthy controls. The authors concluded that pro-inflammatory cytokines are likely to be part of the pathophysiology of emotional disorders in adolescent females, and that SSRIs may exert anti-inflammatory properties in this patient group (Henje Blom et al., 2011).

Cytokine interactions with gonadal hormones

The prevalence of major depression is known to increase during periods of changes in gonadal hormones (Bao et al., 2005). While the male-to-female ratio is 1:1 during childhood, the 1:2 sex ratio that characterizes adult MDD first emerges during adolescence (Birmaher et al., 1996). The timing of the change in male-to-female prevalence ratios for depression has

important implications for theories about the relationship between depression and puberty. Angold et al. reported early the role of secondary sex characteristics in the development of depression (Angold et al., 1998). Characteristics of gender development (sex characteristics) as expressed in Tanner stages ranging from I-prepubertal to V-adult level of development have been suspected to better associate with the development of depression rather than age. It also appeared that this transition in gender prevalence ratios was a mid-pubertal event, occurring in Tanner stage III, generating theories about a role of gonadal hormones in the etiology of depression (Angold et al., 1998). .

Research in pre-menopausal women indicates that gonadal hormones may modulate immune function (Schwarz et al., 1999, Verthelyi, 2001). The cytokine response of peripheral blood monocytes after LPS stimulation in premenopausal women appears to be modulated by the phase of the menstrual cycle (Schwarz et al., 1999). Specifically, a lower release of TNF-α (p<0.05) and IL-6 (not significant) during the luteal phase compared to the follicular phase was reported (Schwarz et al., 1999). Overall, however, findings on cytokine production across the normal menstrual cycle have been inconsistent (O'Brien et al., 2007a) requiring further investigations. In addition, it remains to be examined as to whether such findings derived in adult women would generalize and apply to younger age groups such as adolescents. Systematic research is required to determine if a relationship exists in adolescence between cytokines and hormones that are important for brain development. If such a relationship does exist, it will be important to determine if cytokines modulate gonadal hormones or vice versa.

Differences in the Role of Cytokines in Depression between Adolescents and Adults

In this section, we aim to identify evidence for possible differences and similarities on the role of cytokines in adolescent and adult MDD. It is worthwhile to summarise the findings on the possible involvement of natural killer (NK) cells in adult and adolescent depression as an expression of immune activity in this psychiatric condition. While studies in adult MDD when compared to age consistent controls consistently demonstrate lower NK cell activity (Shain et al., 1991, Kronfol et al., 1989, Nerozzi et al., 1989, Irwin et al., 1990) and reduced number of major lymphocyte subclasses (Schleifer et al., 1984), studies of NK cell activity and lymphocyte subpopulations in adolescent MDD as compared to age consistent controls have yielded contradictory findings (Bartlett et al., 1995, Birmaher et al., 1994, Schleifer et al., 2002, Shain et al., 1991, Targum et al., 1990). Some of these inconsistencies in adolescent MDD might be related to methodologies such as accounting for adverse life events in some studies (Birmaher et al., 1994), or sampling of younger age groups (i.e. inclusion of both children and adolescents) (Bartlett et al., 1995) or gender specific findings in girls (Caserta et al., 2011).

[Insert table 1]

A meta-analysis of studies examining the association between depression in adults and elevated levels of the inflammatory marker CRP have also yielded inconsistent results (Kuo et al., 2005). In adolescents, a large population-based study has found no apparent association between CRP and depressive symptoms (Chaiton et al., 2010). Although this first study indicates there may be a difference between adult and adolescent levels of CRP in depression, problems with this study include a lack of clinical diagnosis. In a meta-analysis of the associations of depression with CRP, IL-6, and IL-1, Howren et al. noted the importance of the method used to assess depression, with larger associations noted in clinical samples and when standard clinical

interviews were used to assess depression (Howren et al., 2009). Copeland et al. used a structured interview to assess depression in a study examining longitudinal pathways between CRP and depression in adolescents and young adults (Copeland et al., 2012). The authors found that cumulative depressive episodes predicted later CRP levels after adjusting for important covariates (covariates of sex, age, body mass index (BMI), current nicotine/ alcohol/ illicit drug use, current medication use, recent health ailments, and current low socioeconomic status) (Copeland et al., 2012).

Heterogeneity in results from both adult and adolescent studies may be due to no consideration of other variables that influence inflammation, such as stressful life events (Miller and Cole, 2012, Danese et al., 2011) . Addressing such a potential confounder, Brambilla et al examined the immune function of children with a first episode of MDD unlikely to have been preceded by stressful events. Contrary to that seen in depressed adults, those children without the experience of stressful life events with MDD had normal IL-1β levels (Brambilla et al., 2004). However, it is likely that several depression studies in adults have not accounted for stressful life events, limiting a direct comparison with the study by Brambilla.

Many studies in adult MDD have reported increased TNF-α compared to controls suggesting a role in the pathophysiology of depression (Tuglu et al., 2003, Leo et al., 2006, Pavon et al., 2006, Kim et al., 2007, Dowlati et al., 2010). However, when studying suicidality in adult MDD, studies on its relationship with cytokines have not always included assessment of TNF-α (Mendlovic et al., 1999, Kim et al., 2008). A study which did include measurements of TNF-α in suicidal adults found increased levels of TNF-α (and IL-6) in suicide attempters compared to non-suicidal depressed patients and healthy controls (Janelidze et al., 2011). In

adolescents, contrasting findings were reported. Gabbay et al found that plasma levels of TNF-α were significantly decreased in suicidal adolescents with MDD compared to a nonsuicidal MDD group (Gabbay et al., 2009b). However, the authors noted their findings should be considered preliminary in view of the small sample size (30 patients, 15 controls), and the substantial percentage (57%) of patients receiving psychotropic medications (Gabbay et al., 2009b). The authors also noted that due to the small sample size, in order to preserve statistical power, a multiple comparison correction was not applied (Gabbay et al., 2009b).

If these findings *in vivo* hold true, postmortem studies suggesting the serotonergic system of the prefrontal cortex (PFC) is implicated in suicide in both adolescents and adults (Mann et al., 1989, Pandey et al., 2002), provide a possible pathway linking TNF-α levels to suicidality (Gabbay et al., 2009b). A proposed mechanism to explain how cytokines may affect behavior is through activation of the enzyme IDO, which results in altered serotonin metabolism (Tonelli et al., 2008, Capuron and Miller, 2004). Specifically, increased 5-HT2A receptor binding has been observed in the PFC of teenage (Pandey et al., 2002) and adult suicide victims (Arango et al., 1997). In addition, serotonin has been observed to be depleted in multiple brain regions, including the frontal cortex, in rodents acutely administered IFN-α by intracerebroventricular injection (Kamata et al., 2000).

Importantly, cytokines in the brain of suicide victims, or subjects with depression, have not been systematically studied (Pandey et al., 2012), and the direction of their association remains to be fully understood. For example, Pandey et al. observed that the mRNA levels of TNF-α, IL-1β, IL-6, and protein levels of TNF-α and IL-1β were significantly increased in Brodmann area 10 of the PFC of teenage suicide victims (compared to controls) (Pandey et al.,

2012). Interestingly, Tonelli et al. found no significant change in TNF-α in male or female adult suicide victims, however observed increased IL-4 in female suicide victims and increased IL-13 in male suicide victims (Tonelli et al., 2008). It is possible that these studies are not directly comparable (Pandey et al 2012; Tonelli et al., 2008), as the pathophysiology of teenage suicide and the role of cytokines in teenage suicide may differ from that in adults (Pandey et al., 2012).

[Insert Table 2 about here]

In summary, studies that provide empirical data for a role of cytokines in adolescent MDD currently show similarities and differences between adolescents and adults, not allowing definite conclusions at this stage. Similarities include increased IL-6 levels, and decreased plasma TRP levels (Gabbay et al., 2009a, Gabbay et al., 2010). Differences in IL-1β variation have been reported, with normal levels in "un-stressed" children with MDD (Brambilla et al., 2004) and elevated levels in adults with MDD (Maes et al., 1991). Plasma TNF-α was noted to be significantly decreased in adolescents with MDD and suicidality (Gabbay et al., 2009b), yet mRNA levels of TNF-α were significantly increased in the PFC of teenage suicide victims (Pandey et al., 2012). A meta-analysis in adults with MDD, regardless of suicidality, suggests a consistent association between circulating levels of TNF-α and adult MDD (Dowlati et al., 2010). Therefore, results for TNF-α are inconsistent between studies, however cytokines have been measured from different sites (for example, plasma in Gabbay et al. 2009b, versus postmortem brain tissue in Pandey et al. 2012). In addition, it remains to be clarified, if suicidality alone could account for the differences in cytokines reported in MDD studies in adults and adolescents.

Small sample sizes in most of the studies on adolescents limit conclusions (e.g. 33 individuals in the Brambilla et al. study, and 45 individuals in the studies by Gabbay et al. 2009a and Gabbay et al. 2009b). Furthermore, there are significant differences between many of the study protocols, such as cross-sectional studies of hospital inpatients (e.g. a proportion of patients in Gabbay et al. 2009a and Gabbay et al. 2009b were inpatients) versus longitudinal population-based observational studies (e.g. Copeland et al. 2012, Miller and Cole, 2012), prohibiting a formal meta-analysis. Further research using epidemiological approaches (Dantzer, 2012) in well-powered and well-designed cohorts is required to provide empirical data to consolidate and build on these results.

[Insert table 3 about here]

III.   Clinical Implications

Antidepressant drugs appear to have some action on pro-inflammatory cytokines (Bengtsson et al., 1992, Xia et al., 1996), with attenuation of an imbalance between pro- and anti-inflammatory cytokines in patients with MDD treated with the antidepressants fluoxetine, sertraline, or paroxetine (Kim et al., 2007, Kubera et al., 2000, Sutcigil et al., 2007, Taler et al., 2007, Tuglu et al., 2003). Furthermore, patients who fail to respond to antidepressants have been found to demonstrate increased plasma concentrations of IL-6 and acute phase reactants when compared to treatment-responsive patients (Sluzewska et al., 1997, Maes et al., 1997, O'Brien et al., 2007b).

Other agents and treatment programs that have anti-inflammatory actions or block actions of cytokines, such as physical exercise and omega-3 polyunsaturated fatty acids, may

have a role in the treatment of depression. It is possible that physical exercise may exert similar anti-inflammatory effects beneficial to improving depressive symptoms, which are believed to be more globally mediated through various pathways of the neuroimmune system (Eyre and Baune, 2011). As recently extensively reviewed by these authors, consistent exercise / physical activity has been shown to reduce levels of IL-1β, TNF-α, IL-6, and CRP (Eyre and Baune, 2011), whereas studies examining the cytokine levels during or immediately after exercise have shown an upregulation of IL-6 and IL-8 (Fischer, 2006, Pedersen, 2009). The short-term effects of exercise with an acute transient upregulation of IL-6 appears to induce a rise in IL-10 (Steensberg et al., 2003), and to negate neurotoxic changes of TNF-α (Funk et al., 2011). Further research has been recommended to enhance alternative treatment approaches to depression, such as physical exercise, that might improve depression via the immune system (Eyre and Baune, 2011).

A meta-analysis of 10 double-blind, placebo-controlled studies in adult patients with mood disorders receiving omega-3 PUFAs, indicated an antidepressant effect of omega-3 PUFAs (Lin and Su, 2007). However, the authors noted that it is premature to draw firm conclusions based on the findings due to the heterogeneity of the different study methodologies (Lin and Su, 2007). Similar effects have also been reported for children in a small randomized controlled trial study showing that long chain omega-3 PUFAs supplementation in the treatment of children with a first episode of depression had a benefit in reducing depressive symptoms, however not in achieving remission (Nemets et al., 2006). Given the implication of omega-3 PUFAs in depression, it is therefore interesting that omega-3 PUFAs have the capacity to decrease the production of pro-inflammatory cytokines, and exert strong anti-inflammatory

effects (Maes et al., 2009); studies in adolescents could add valuable knowledge to the literature.

In studies of adults with depression, cytokine antagonists have also been found to have antidepressant-like effects (Mendlewicz et al., 2006, Krishnan et al., 2007, Tyring et al., 2006, Yirmiya, 2000, Raison et al., 2012, Dantzer et al., 1999). TNF-α blockers such as etanercept and infliximab have been found to attenuate the depressive symptoms that accompany immune system activation in psoriasis (Krishnan et al., 2007, Tyring et al., 2006, Yirmiya, 2000, Dantzer et al., 1999). However, conflicting results have been reported for TNF-α antagonists such as infliximab in that depressed patients with higher levels of CRP prior to treatment may benefit from such treatment as opposed to a general benefit in depression (Raison et al., 2012).

Anti-inflammatory medications have also been found to have antidepressant-like effects. For example, acetylsalicylic acid added to fluoxetine led to increased remission rates in depressed patients previously unresponsive to fluoxetine alone (Mendlewicz et al., 2006). Furthermore, in patients with MDD adding the cyclooxygenase-2 (COX-2) inhibitor celecoxib to treatment with reboxetine (Muller et al., 2006) or sertraline (Abbasi et al., 2012) induced an antidepressant response. Interestingly, Abbasi et al. also showed a significantly greater reduction in serum IL-6 concentrations in the group treated with celecoxib and sertraline (compared to the group treated with sertraline) (Abbasi et al., 2012) .

It has been noted that selectively targeting COX-2 in the treatment of depression may be problematic (Maes, 2012). Consistent with determining the mechanism of action of COX-2 inhibitors in depression, Maes reviewed possible detrimental effects of COX-2 inhibitors targeting pathways involved in depression. He concluded that treatments with COX-2 inhibitors

may aggravate the pathophysiology of depression, through involvement in pathways which include lowering of antioxidant defenses and inducing neuroinflammation (Maes, 2012). As anti-inflammatory treatments and the use of cytokine antagonists are less common in adolescents than in adults, further research is required to determine if interventions that act on immune responses are effective interventions for depression in adolescent populations.

Conclusion

A substantial body of literature has now focused on the association between cytokines and depression, primarily in adults with less extensive research in adolescents (Sharpley and Agnew, 2011). However, this review shows that the role of cytokines in adolescent depression is characterized by many similarities with adult MDD, although important differences of cytokines in depression between these age groups may be emerging.

The relatively small number of studies on the role of cytokines in adolescent MDD has to be taken into account alongside with several methodological issues, which limit their comparability among studies in adolescents but also with research in adults. In general, the sample sizes of these studies are small and few have employed a prospective design. This could particularly be an issue if altered cytokine levels are a consequence of illness, rather than a cause. If this is the case, altered cytokine levels in adolescence would be more subtle, and so larger sample numbers would be required to detect them statistically, compared to adult studies where changes might be more established and pronounced.

Depression in children and adolescents show some different immune and inflammatory changes to those seen in adult depression in the current literature, with contradictory findings of NK cell activity, and differences in pro-inflammatory cytokines such as IL-1β and TNF-α (Shain et al., 1991, Brambilla et al., 2004, Gabbay et al., 2009b, Pandey et al., 2012). Some of the reported differences between the role of cytokines in depression could be influenced by neurodevelopment, hormonal changes, stress, and trauma, with more direct effects in young individuals as they experience developmental changes compared to adults. An improved understanding of the role of cytokines in adolescent MDD also in relation to stress, maltreatment, hormonal changes and genetic background may inform aetiology and treatment options in adolescent depression.

Further research is warranted to explore more broadly the role of cytokines in depression of adolescents considering adequately the neurobiological, hormonal and environmental changes young individuals are undergoing. Moreover, additional treatment options might be suitable in some forms of inflammation associated depression in adolescents. Initially, the field could be progressed with the inclusion of measurements of circulating cytokines, such as IL-1β, IL-6, and TNF-α, in intervention studies in adolescent MDD. Later, interventions that change levels of circulating plasma cytokines in adolescents with MDD may prove worthy of investigation. Importantly, future research requires well-designed, well-powered clinical studies that consider environmental factors (in particular stressful life events), in addition to using genetic, developmentally, and physiologically sensitive designs with prospective community-based studies, as well as psychiatric samples (Goodyer, 2008).

Acknowledgements

Conflict of Interest

None

- Cytokines mediate key steps in cellular and humoral immunity
- Immune system dysregulation / pro- inflammatory cytokines have been implicated in adult major depressive disorder (MDD)
- Studies on the role of cytokines in adolescent MDD are few; the immune / inflammatory changes seen in adolescent MDD show specific similarities and differences to those seen in adult MDD
- Cytokines may influence neurodevelopment during adolescence
- Potential treatments that modify inflammation require further research, as this may lead to better outcomes in the treatment of adolescent MDD

References

ABBASI, S.-H., HOSSEINI, F., MODABBERNIA, A., ASHRAFI, M. & AKHONDZADEH, S. (2012). Effect of celecoxib add-on treatment on symptoms and serum IL-6 concentrations in patients with major depressive disorder: Randomized double-blind placebo-controlled study. *Journal of Affective Disorders,* 141**,** 308-314.

ANDRADE, L., CARAVEO-ANDUAGA, J., BERGLUND, P., BIJL, R., DE GRAAF, R., VOLLEBURGH, W., DRAGOMIRECKA E, KOHN, R., KELLER, M., KESSLER, R., KAWAKAMI, N., KILIC, C., OFFORD, D., USTUN, T. & WITTCHEN, H. (2003). The epidemiology of major depressive epiosodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. *Int J Methods Psychiatr Res,* 12**,** 3-21.

ANGOLD, A., COSTELLO, E. & WORTHMAN, C. (1998). Puberty and depression: the roles of age, pubertal status and pubertal timing. *Psychological Medicine,* 28**,** 51-61.

APA (2000). *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR),* Washington, DC.

APA (2011). DSM-5 Development. (pp. Retreived from http://www.dsm5.org (7/3/13)).

ARANGO, V., UNDERWOOD, M. & MANN, J. (1997). Postmortem findings in suicide victims. Implications for in vivo imaging studies. *Ann N Y Acad Sci,* 836**,** 269-287.

BABCOCK, T. & CARLIN, J. (2000). Transcriptional activation of indoleamine dioxygenase by interleukin 1 and tumor necrosis factor alpha in interferon-treated epithelial cells. *Cytokine,* 12**,** 588-594.

BANKS, W., KASTIN, A. & DURHAM, D. (1989). Bidirectional transport of interleukin-1 alpha across the blood-brain barrier. *Brain Res Bull,* 23**,** 433-437.

BAO, A.-M., HESTIANTORO, A., VAN SOMERON, E. J. W., SWAAB, D. F. & ZHOU, J.-N. (2005). Colocalization of corticotropin-releasing hormone and oestrogen receptor-alpha

in the paraventricular nucleus of the hypothalamus in mood disorders. *Brain* 128**,** 1301-1313.

BARTLETT, J., SCHLEIFER, S., DEMETRIKOPOULOS, M. & KELLER, S. (1995). Immune differences in children with and without depression. *Biol Psychiatry,* 38**,** 771-774.

BAUNE, B. T., DANNLOWSKI, U., DOMSCHKE, K., JANSSEN, D. G. A., JORDAN, M. A., OHRMANN, P., BAUER, J., BIROS, E., AROLT, V., KUGEL, H., BAXTER, A. G. & SUSLOW, T. (2010). The Interleukin 1 Beta (*IL 1B*) Gene Is Associated with Failure to Achieve Remission and Impaired Emotion Processing in Major Depression. *Biological Psychiatry,* 67**,** 543-549.

BAUNE, B. T., KONRAD, C., GROTEGERD, D., SUSLOW, T., BIROSOVA, E., OHRMANN, P., BAUER, J., AROLT, V., HEINDEL, W., DOMSCHKE, K., SCHONING, S., RAUCH, A. V., UHLMANN, C., KUGEL, H. & DANNLOWSKI, U. (2012a). Interleukin-6 gene (*IL-6*): a possible role in brain morphology in the healthy adult brain. *Journal of Neuroinflammation,* 9**,** Article Number 125.

BAUNE, B. T., KONRAD, C., GROTEGERD, D., SUSLOW, T., OHRMANN, P., BAUER, J., AROLT, V., HEINDEL, W., DOMSCHKE, K., SCHONING, S., RAUCH, A. V., SEHLMEYER, C., KUGEL, H. & DANNLOWSKI, U. (2012b). Tumor Necrosis Factor Gene Variation Predicts Hippocampus Volume in Healthy Individuals. *Biol Psychiatry,* 72**,** 655-662.

BAUNE, B. T., SMITH, E., REPPERMUND, S., AIR, T., SAMARAS, K., LUX, O., BRODATY, H., SACHDEV, P. & TROLLOR, J. N. (2012c). Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: The prospective Sydney Memory and Aging Study. *Psychoneuroendocrinology,* in press.

BENES, F. M. (1989). Myelination of Cortical-Hippocampal Relays During Late Adolescence. *Schizophrenia Bulletin,* 15**,** 585-593.

BENGTSSON, B., ZHU, J., THORELL, L., OLSSON, T., LINK, H. & WALINDER, J. (1992). Effects of zimeldine and its metabolites, clomipramine, imipramine, and maprotiline in experimental allergic neuritis in Lewis rats. *J Neuroimmunol,* 39**,** 109-122.

BET, P. M., PENNINX, B. W. J. H., BOCHDANOVITS, Z., UITTERLINDEN, A. G., BEEKMAN, A. T. F., VAN SCHOOR, N. M., DEEG, D. J. H. & HOOGENDIJK, W. J. G. (2008). Glucocorticoid Receptor Gene Polymorphisms and Childhood Adversity Are Associated With Depression: New Evidence for a Gene-Environment Interaction. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics,* 150B**,** 660-669.

BIRMAHER, B., RABIN, B., GARCIA, M., JAIN, U., WHITESIDE, T., WILLIAMSON, D., SHABBOUT, M., NELSON, B., DAHL, R. & RYAN, N. (1994). Cellular Immunity in Depressed, Conduct Disorder, and Normal Adolescents: Role of Adverse Life Events. *Journal American Academy of Child and Adolescent Psychiatry,* 33**,** 671-678.

BIRMAHER, B., RYAN, N. & WILLIAMSON, D. E. A. (1996). Childhood and adolescent depression: a review of the past ten years. Part I. *Journal American Academy of Child and Adolescent Psychiatry,* 35**,** 1427-1439.

BLUTHE, R., WALTER, V., PARNET, P., LAYE, S., LESTAGE, J., VERRIER, D., POOLE, S., STENNING, B., KELLEY, K. & DANTZER, R. (1994). Lipopolysaccharide induces sickness behaviour in rats by a vagal mediated mechanism. *C R Acad Sci III,* 317**,** 499-503.

BRAMBILLA, F., MONTELEONE, P. & MAJ, M. (2004). Interleukin-1B and tumor necrosis factor-alpha in children with major depressive disorder or dysthymia. *Journal of Affective Disorders,* 78**,** 273-277.

BREDER, C., DINARELLO, C. & SAPER, C. (1988). Interleukin-1 immunoreactive innervation of the human hypothalamus. *Science,* 240**,** 321-324.

BUFALINO, C., HEPGUL, N., AGUGLIA, E. & PARIANTE, C. M. (2012). The role of immune genes in the association between depression and inflammation: A review of recent clinical studies. *Brain, Behavior, and Immunity,* In Press.

CAO, C., MATSUMURA, K., YAMAGATA, K. & WATANABE, Y. (1997). Involvement of cyclooxygenase-2 in LPS-induced fever and regulation of its mRNA by LPS in the rat brain. *Am J Physiol,* 272**,** R1712-R1725.

CAPURON, L. & MILLER, A. H. (2004). Cytokines and Psychopathology: Lessons from Interferon-alpha. *Biological Psychiatry,* 56**,** 819-824.

CAPURON, L. & MILLER, A. H. (2011). Immune system to brain signaling: Neuropsychopharmacological implications. *Pharmacology & Therapeutics,* 130**,** 226-238.

CAPURON, L., RAISON, C. L., MUSSELMAN, D. L., LAWSON, D. H., NEMEROFF, C. B. & MILLER, A. H. (2003). Association of Exaggerated HPA Axis Response to the Initial Injection of Interferon-Alpha With Development of Depression During Interferon-Alpha Therapy. *Am J Psychiatry,* 160**,** 1342-1345.

CARLEZON JR., W. & NESTLER, E. (2002). Elevated levels of GluR1 in the midbrain: a trigger for sensitization to drugs of abuse? *Trends in Neurosciences,* 25**,** 610-615.

CASERTA, M. T., WYMAN, P. A., WANG, H., MOYNIHAN, J. & O'CONNOR, T. G. (2011). Associations among depression, perceived self-efficacy, and immune function and health in preadolescent children. *Development and Psychopathology,* 23**,** 1139-1147.

CASPI, A., SUGDEN, K. & AL., M. T. E. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science,* 301**,** 386-389.

CAVANAGH, J. & MATHIAS, C. (2008). Inflammation and its relevance to psychiatry. *Advances in Psychiatric Treatment,* 14**,** 248-255.

CHAITON, M., O'LOUGHLIN, J., KARP, I. & LAMBERT, M. (2010). Depressive Symptoms and C-Reactive Protein Are Not Associated in a Population-Based Sample of Adolescents. *Int J Behav Med,* 17**,** 216-222.

CONNOR, T. & LEONARD, B. (1998). Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Sciences,* 62**,** 583-606.

COPELAND, W. E., SHANAHAN, L., WORTHMAN, C., ANGOLD, A. & COSTELLO, E. J. (2012). Cumulative Depression Episodes Predict Later C-Reactive Protein Levels: A Prospective Analysis. *Biological Psychiatry,* 71**,** 15-21.

D'MELLO, C., LE, T. & SWAIN, M. (2009). Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factor alpha signaling during peripheral organ inflammation. *J Neurosci,* 29**,** 2089-2102.

DANESE, A., CASPI, A., WILLIAMS, B., AMBLER, A., SUGDEN, K., MIKA, J., WERTS, H., FREEMAN, J., PARIANTE, C., MOFFITT, T. & ARSENEAULT, L. (2011). Biological embedding of stress through inflammation processes in childhood. *Molecular Psychiatry,* 16**,** 244-246.

DANESE, A., MOFFITT, T. E., PARIANTE, C. M., AMBLER, A., POULTON, R. & CASPI, A. (2008). Elevated Inflammation Levels in Depressed Adults With a History of Childhood Maltreatment. *Arch Gen Psychiatry,* 65**,** 409-416.

DANESE, A., PARIANTE, C. M., CASPI, A., TAYLOR, A. & POULTON, R. (2007). Childhood maltreatment predicts adult inflammation in a life-course study. *Proc Natl Acad Sci USA,* 104**,** 1319-1324.

DANTZER, R. (2009). Cytokine, Sickness Behavior, and Depression. *Immunology and Allergy Clinics of North America,* 29**,** 247-264.

DANTZER, R. (2012). Depression and Inflammation: An Intricate Relationship. *Biological Psychiatry,* 71**,** 4-5.

DANTZER, R., AUBERT, A., BLUTHE, R. M., GHEUSI, G., CREMONA, S., LAYE, S., KONSMAN, J. P., PARNET, P. & KELLEY, K. W. (1999). Mechanisms of the behavioural effects of cytokines. In R. DANTZER, E. E. WOLLMAN & R. YIRMIYA (Eds.) *Cytokines, Stress, and Depression.* (pp. 83-105).

DANTZER, R., O'CONNOR, J., FREUND, G., JOHNSON, R. & KELLEY, K. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Reviews Neuroscience,* 9**,** 46-57.

DE CRAEN, A., POSTHUMA, D., REMARQUE, E., VAN DEN BIGGELAAR, A. & WESTENDORP, R. (2005). Heritability estimates of innate immunity: an extended twin study. *Genes and Immunity,* 6**,** 167-170.

DE ROOIJ, S. R., COSTELLO, P. M., VEENENDAAL, M. V., LILLYCROP, K. A., GLUCKMAN, P. D., HANSON, M. A., PAINTER, R. C. & ROSEBOOM, T. J. (2012). Associations between DNA methylation of a glucocorticoid receptor promoter and acute stress responses in a large healthy adult population are largely explained by lifestyle and educational differences. *Psychoneuroendocrinology,* 37**,** 782-788.

DEINZER, R., GRANRATH, N., STUHL, H., TWORK, L., IDEL, H., WASCHUL, B. & HERFORTH, A. (2004). Acute stress effects on local IL-1beta responses to pathogens in a human in vivo model. *Brain Behav Immun,* 18**,** 458-467.

DIXON, D., MENG, H., GOLDBERG, R., SCHNEIDERMAN, N. & DELAMATER, A. (2009). Stress and body mass index each contributes independently to tumor necrosis factor-[alpha] production in prepubescent latino children. *J. Paediatr. Nurs.,* 24**,** 378-388.

DOWLATI, Y., HERRMAN, N., SWARDFAGER, W., LIU, H., SHAM, L., REIM, E. K. & LANCTOT, K. L. (2010). A Meta-Analysis of Cytokines in Major Depression. *Biological Psychiatry,* 67**,** 446-457.

DU, J., CRESON, T., WU, L., REN, M., GRAY, N., FALKE, C., WEI, Y., WANG, Y., BLUMENTHAL, R. & MACHADO-VIEIRA, R., ET AL. (2008). The role of hippocampal GluR1 and GluR2 receptors in manic-like behavior. *Journal of Neuroscience,* 28**,** 68-79.

DU, J., GRAY, N., FALKE, C., CHEN, W., YUAN, P., SZABO, S., EINAT, H. & MANJI, H. (2004). Modulation of synaptic plasticity by antimanic agents: the role of AMPA glutamate receptor subunit 1 synaptic expression. *Journal of Neuroscience,* 24**,** 6578-6589.

DU, J., SUZUKI, K., WEI, Y., WANG, Y., BLUMENTHAL, R., CHEN, Z., FALKE, C., ZARATE JR., C. & MANJI, H. (2007). The anticonvulsants lamotrigine, riluzole, and valproate differentially regulate AMPA receptor membrane localization: relationship to clinical effects in mood disorders. *Neuropsychopharmacology,* 32**,** 793-802.

DUNN, V. & GOODYER, I. M. (2006). Longitudinal investigation into childhood- and adolescence-onset depression: psychiatric outcome in early adulthood. *British Journal of Psychiatry,* 188**,** 216-222.

EINVIK, G., VISTNES, M., HRUBOS-STROM, H., RANDBY, A., NAMTVEDT, S. K., NORDHUS, I. H., SOMERS, V. K., DAMMEN, T. & OMLAND, T. (2012). Circulating cytokine concentrations are not associated with major depressive disorder in a community-based cohort. *General Hospital Psychiatry,* 34**,** 262-267.

ERICSSON, A., KOVACS, K. & PE, S. (1994). A functional anatomical analysis of central pathways subserving the effects of interleukin-1 on stress-related neuroendocrine neurons. *J Neurosci,* 14**,** 897-913.

EYRE, H. & BAUNE, B. T. (2011). Neuroimmunological effects of physical exercise in depression. *Brain, Behavior, and Immunity,* 26**,** 251-266.

EYRE, H. & BAUNE, B. T. (2012). Neuroplastic changes in depression: A role for the immune system. *Psychoneuroendocrinology,* 37**,** 1397-1416.

FABRY, Z., FITZSIMMONS, K., HERLEIN, J., MONINGER, T., DOBBS, M. & HART, M. (1993). Production of the cytokines interleukin 1 and 6 by murine brain microvessel endothelium and smooth muscle pericytes. *J Neuroimmunol,* 47**,** 23-34.

FAGUNDES, C. P., GLASER, R. & KIECOLT-GLASER, J. K. (2013). Stressful early life experiences and immune dysregulation across the lifespan. *Brain, Behavior, and Immunity,* 27**,** 8-12.

FERTUZINHOS, S. M. M., OLIVEIRA, J. R. M., NISHIMURA, A. L., PONTUAL, D., CARVALHO, D. R., SOUGEY, E. B., OTTO, P. A. & ZATZ, M. (2004). Analysis of IL-1 alpha, IL-1 beta, and IL-RA polymorphisms in dysthymia. *Journal of Molecular Neuroscience,* 22**,** 251-255.

FISCHER, C. P. (2006). Interleukin-6 in acute exercise and training: what is the biological relevance? *Exerc Immunol Rev,* 12**,** 6-33.

FISHER, H. L., COHEN-WOODS, S., HOSANG, G. M., UHER, R., POWELL-SMITH, G., KEERS, R., TROPEANO, M., KORSZUN, A., JONES, L., JONES, I., OWEN, M., CRADDOCK, N., CRAIG, I. W., FARMER, A. E. & MCGUFFIN, P. (2012). Stressful life events and the serotonin transporter gene (*5-HTT*) in recurrent clinical depression. *Journal of Affective Disorders,* 136**,** 189-193.

FRENOIS, F., MOREAU, M., O'CONNOR, J., LAWSON, M., MICON, C., LESTAGE, J., KELLEY, K. W., DANTZER, R. & CASTANON, N. (2007). Lipopolysaccharide induces delayed FosB/DeltaFosB immunostaining within the mouse extended amygdala, hippocampus and hypothalamus, that parallel the expression of depressive-like behavior. *Psychoneuroendocrinology,* 32**,** 516-531.

FUNK, J., GOHLKE, J. & AL., E. (2011). Voluntary exercise protects hippocampal neurons from trimethyltin injury: possible role of interleukin-6 to modulate tumor necrosis factor receptor-mediated neurotoxicity. *Brain Behav Immun,* 25**,** 1063-1077.

GABBAY, V., KLEIN, R. G., ALONSO, C. M., BABB, J. S., NISHAWALA, M., DE JESUS, G., HIRSCH, G. S., HOTTINGER-BLANC, P. M. Z. & GONZALEZ, C. J. (2009a). Immune system dysregulation in adolescent major depressive disorder. *Journal of Affective Disorders,* 115**,** 177-182.

GABBAY, V., KLEIN, R. G., GUTTMAN, L. E., BABB, J. S., ALONSO, C. M., NISHAWALA, M., KATZ, Y., GAITE, M. R. & GONZALEZ, C. J. (2009b). A

Preliminary Study of Cytokines in Suicidal and Nonsuicidal Adolescents with Major Depression. *Journal of Child and Adolescent Psychopharmacology,* 19**,** 423-430.

GABBAY, V., KLEIN, R. G., KATZ, Y., MENDOZA, S., GUTTMAN, L. E., ALONSO, C. M., BABB, J. S., HIRSCH, G. S. & LIEBES, L. (2010). The possible role of the kynurenine pathway in adolescent depression with melancholic features. *Journal of Child Psychology and Psychiatry,* 51**,** 935-943.

GIMENO, D., KIVIMAKI, M., BRUNNER, E., ELOVAINIO, M., DE VOGLI, R., STEPTOE, A., KUMARI, M., LOWE, G., RUMLEY, A., MARMOT, M. & FERRIE, J. (2009). Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychol Med,* 39**,** 413-423.

GODBOUT, J. & JOHNSON, R. (2004). Interleukin-6 in the aging brain. *J Neuroimmunol,* 147**,** 141-144.

GOEBEL, M., MILLS, P., IRWIN, M. & ZIEGLER, M. (2000). Interleukin-6 and tumor necrosis factor-alpha production after acute psychological stress, exercise, and infused isoproterenol: differential effects and pathways. *Psychosom Med,* 62**,** 591-598.

GOLDSTEIN, L., LEOPOLD, M., HUANG, X., ATWOOD, C., SAUNDERS, A., HARTSHORN, M., LIM, J., FAGET, K., MUFFAT, J., SCARPA, R., CHYLACK, L. J., BOWDEN, E., TANZI, R. & BUSH, A. (2000). 3-Hydroxykynurenine and 3-hydroxyanthranilic acid generate hydrogen peroxide and promote alpha-crystallin cross-linking by metal ion reduction. *Biochemistry,* 39**,** 7266-7275.

GOODYER, I. (2008). Emmanuel Miller Lecture: Early onset depressions - meanings, mechanisms and processes. *The Journal of Child Psychology and Psychiatry,* 49**,** 1239-1256.

HAROON, E., RAISON, C. & MILLER, A. (2011). Psychoneuroimmunology Meets Neuropsychopharmacology: Translational Implications of the Impact of Inflammation on Behavior. *Neuropsychopharmacology Reviews***,** 1-26.

HENJE BLOM, E., LEKANDER, M., INGVAR, M., ASBERG, M., MOBARREZ, F. & SERLACHIUS, E. (2011). Pro-inflammatory cytokines are elevated in adolescent females with emotional disorders not treated with SSRIs. *J Affect Disord,* 136**,** 716-723.

HILL, J., PICKLES, A., ROLLINSON, L., DAVIES, R. & BYATT, M. (2004). Juvenile- *versus* adult-onset depression: multiple differences imply different pathways. *Psychological Medicine,* 34**,** 1483-1493.

HOOD, K. K., LAWRENCE, J. M., ANDERSON, A., BELL, R., DABALEA, D., DANIELS, S., RODRIGUEZ, B. & DOLAN, L. M. (2012). Metabolic and Inflammatory Links to Depression in Youth With Diabetes. *Diabetes Care,* 35**,** 2443-2446.

HOWREN, M., LAMKIN, D. & SULS, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosom Med,* 71**,** 171-186.

IRWIN, M. & MILLER, A. (2007). Depressive disorders and immunity:20 years of progress and discovery. . *Brain, Behavior, and Immunity,* 21**,** 374-383.

IRWIN, M., PATTERSON, T. & SMITH, T. E. A. (1990). Reduction of immune function in life stress and depression. *Biol Psychiatry,* 27**,** 22-30.

JAFFEE, S. R., MOFFITT, T. E., CASPI, A., FOMBONNE, E., POULTON, R. & MARTIN, J. (2002). Differences in Early Childhood Risk Factors for Juvenile-Onset and Adult-Onset Depression. *Archives of General Psychiatry,* 58**,** 215-222.

JANELIDZE, S., MATTEI, D., WESTRIN, A., TRASKMAN-BENDZ, L. & BRUNDIN, L. (2011). Cytokine levels in the blood may distinguish suicide attempters from depressed patients. *Brain, Behavior, and Immunity,* 25**,** 335-339.

JANSSEN, D., CANIATO, R., VERSTER, J. & BAUNE, B. (2010). A psychoneuroimmunological review on cytokines involved in antidepressant treatment response. *Human Psychopharmacology-Clinical and Experimental,* 25**,** 1-15.

JUN, T., PAE, C., HOON, H., CHAE, J., BAHK, W., KIM, K. & SERRETTI, A. (2003). Possible association between G308A tumour necrosis factor-alpha gene polymorphism and major depressive disorder in the Korean population. *Psychiatric Genetics,* 13**,** 179-181.

KAMATA, M., HIGUCHI, H., YOSHIMOTO, M., YOSHIDA, K. & SHIMIZU, T. (2000). Effect of single intracerebroventricular injection of alpha-interferon on monoamine concentrations in the rat brain. *Eur Neuropsychopharmacol,* 10**,** 129-132.

KARG, K., BURMEISTER, M., SHEDDEN, K. & SEN, S. (2011). The Serotonin Transporter Promoter Variant (5-HTTLPR), Stress, and Depression Meta-analysis Revisited: Evidence of Genetic Moderation. *Arch Gen Psychiatry,* 68**,** 444-454.

KAUFMAN, J., MARTIN, A., KING, R. A. & CHARNEY, D. (2001). Are child-, adolescent-, and adult-onset depression one and the same disorder? *Biological Psychiatry,* 49**,** 980-1001.

KENDELL, S., KRYSTAL, J. & SANACORA, G. (2005). GABA and glutamate systems as therapeutic targets in depression and mood disorders. *Expert Opinion on Therapeutic Targets,* 9**,** 153-168.

KENT, S., BLUTHE, R., KELLEY, K. & DANTZER, R. (1992). Sickness behavior as a new target for drug development. *Trends Pharmacol. Sci.,* 13**,** 24-28.

KHAIROVA, R., MACHADO-VIEIRA, R., DU, J. & MANJI, H. (2009). A potential role for pro-inflammatory cytokines in regulating synaptic plasticity in major depressive disorder. *International Journal of Neuropsychopharmacology,* 12**,** 561-578.

KILBOURN, R. G. & BELLONI, P. (1990). Endothelial Cell Production of Nitrogen Oxides in Response to Interferon gamma in Combination With Tumor Necrosis Factor, Interleukin-1, or Endotoxin. *Journal of the National Cancer Institute,* 82**,** 772-776.

KIM, Y., LEE, S., KIM, S., SHIM, S., HAN, S., CHOI, S. & LEE, B. (2008). Differences in cytokines between non-suicidal patients and suicidal patients in major depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry,* 32**,** 356-361.

KIM, Y., NA, K., SHIN, K., JUNG, H., CHOI, S. & KIM, J. (2007). Cytokine imbalance in the pathophysiology of major depressive disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry,* 31**,** 1044-1053.

KOMAKI, G., ARIMURA, A. & KOVES, K. (1992). Effect of intravenous injection of IL-1 beta on PGE2 levels in several brain areas as determined by microdialysis. *Am J Physiol,* 262**,** E246-E251.

KOO, J. & DUMAN, R. (2008). IL-1beta is an essential mediator of the antineurogenic and anhedonic effects of stress. *Proc Natl Acad Sci U S A,* 105**,** 751-756.

KOVACS, M. (1996). Presentation and course of major depressive disorder during childhood and later years of the life span. *J Am Acad Child Adolesc Psychiatry,* 35**,** 705-715.

KRISHNAN, R., CELLA, D., LEONARDI, C., PAPP, K., GOTTLIEB, A., DUNN, M., CHIOU, C., PATEL, V. & JAHREIS, A. (2007). Effects of etanercept therapy on fatigue and

symptoms of depression in subjects treated for moderate to severe plaque psoriasis for up to 96 weeks. *British Journal of Dermatology,* 157**,** 1275-1277.

KRONFOL, Z., NAIR, M., GOODSON, J., GOEL, K., HASKETT, R. & SCHWARTZ, S. (1989). Natural killer cell activity in depressive illness: A preliminary report. *Biol Psychiatry,* 26**,** 753-756.

KRONFOL, Z. & REMICK, D. (2000). Cytokines and the Brain: Implications for Clinical Psychiatry. *American Journal of Psychiatry,* 157**,** 683-694.

KUBERA, M., KENIS, G., BOSMANS, E., ZIEBA, A., DUDEK, D., NOWAK, G. & MAES, M. (2000). Plasma levels of interleukin-6, interleukin-10, and interleukin-1 receptor antagonist in depression: comparison between the acute state and after remission. *Polish Journal of Pharmacology,* 52**,** 237-241.

KUO, H.-K., YEN, C.-J., CHANG, C.-H., KUO, C.-K., CHEN, J.-H. & SOROND, F. (2005). Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: systematic review and meta-analysis. *Lancet Neurol,* 4**,** 371-380.

LEO, R., DI LORENZO, G., TESAURO, M., RAZZINI, C., FORLEO, G., CHIRICOLO, G., COLA, C., ZANASI, M., TROISI, A., SIRACUSANO, A., LAURO, R. & ROMEO, F. (2006). Association between enhanced soluble CD40 ligand and proinflammatory and prothrombotic states in major depressive disorder:Pilot observations on the effects of selective serotonin reuptake inhibitor therapy. *J Clin Psychiatry,* 67**,** 1760-1766.

LIBERATI, A., ALTMAN, D. G., TETZLAFF, J., MULROW, C., GOTZSCHE, P. C., IOANNIDIS, J. P., CLARKE, M., DEVEREAUX, P. J., KLEIJNEN, J. & MOHER, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ,* 339:b2700.

LIN, P. & SU, K. (2007). A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. *J Clin Psychiatry,* 68**,** 1056-1061.

LOFTIS, J. M., HUCKANS, M. & MORASCO, B. J. (2010). Neuroimmune mechanisms of cytokine-induced depression: Current theories and novel treatment strategies. *Neurobiology of Disease,* 37**,** 519-533.

MADRIGAL, J., HURTADO, O., MORO, M., LIZASOAIN, I., LORENZO, P., CASTRILLO, A., BOSCA, L. & LEZA, J. (2002). The increase in TNF-alpha levels is implicated in NF-kappaB activation and inducible nitric oxide synthase expression in brain cortex after immobilization stress. *Neuropsychopharmacology,* 26**,** 155-163.

MAES, M. (2012). Targeting cyclooxygenase-2 in depression is not a viable therapeutic approach and may even aggravate the pathophysiology underpinning depression. *Metab Brain Dis,* 27**,** 405-413.

MAES, M., BOSMANS, E., DE JONGH, R., KENIS, G., VANDOOLAEGHE, E. & NEELS, H. (1997). Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine,* 9**,** 853-858.

MAES, M., BOSMANS, E., SUY, E., VANDERVORST, C., DEJONCKHEERE, C. & RAUS, J. (1991). Depression-related disturbances in mitogen-induced lymphocyte responses and interleukin-1beta and soluble interleukin-2 receptor production. *Acta Psychiatrica Scandinavica,* 84**,** 379-386.

MAES, M., JACOBS, M.-P., SUY, E., MINNER, B., LECLERCQ, C., CHRISTIAENS, F. & RAUS, J. (1990). Suppressant effects of dexamethasone on the availability of plasma L-

tryptophan and tyrosine in healthy controls and in depressed patients. *Acta Psychiatrica Scandinavica,* 81**,** 19-23.

MAES, M., MELTZER, H., SCHARPE, S., BOSMANS, E., SUY, E., DE MEESTER, I., CALABRESE, J. & COSYNS, P. (1993). Relationships between lower plasma L-tryptophan levels and immune-inflammatory variables in depression. *Psychiatr. Res.,* 49**,** 151-165.

MAES, M., WAUTERS, A., VERKERK, R., DEMEDTS, P., NEELS, H., VAN GASTEL, A., COSYNS, P., SCHARPE, S. & DESNYDER, R. (1996). Lower serum L-tryptophan availability in depression as a marker of a more generalized disorder in protein metabolism. *Neuropsychopharmacology,* 15**,** 243-251.

MAES, M., YIRMYIA, R., NORABERG, J., BRENE, S., HIBBELN, J., PERINI, G., KUBERA, M., BOB, P., LERER, B. & MAJ, M. (2009). The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depresssion. *Metabolic Brain Disease,* 24**,** 27-53.

MALENKA, R. (2003). The long-term potential of LTP. *Nature Reviews Neuroscience,* 4**,** 923-926.

MANN, J., ARANGO, V., MARZUK, P., THECCANAT, S. & REIS, D. (1989). Evidence for the 5-HT hypothesis of suicide. A review of post-mortem studies. *British Journal of Psychiatry,* 155**,** 7-14.

MCCRORY, E., DE BRITO, S. A. & VIDING, E. (2010). Research Review: The neurobiology and genetics of maltreatment and adversity. *The Journal of Child Psychology and Psychiatry,* 51**,** 1079-1095.

MCDERMOTT, B., BAIGENT, M., CHANEN, A., FRASER, L., GRAETZ, B., HAYMAN, N., NEWMAN, L., PARIKH, N., PEIRCE, B., PROIMOS, J., SMALLEY, T., SPENCE, S. & COMMITTEE, *B.* E. W. (2010). Clinical practice guidelines: depression in adolescents and young adults. Melbourne: *beyondblue:* the national depression initiative.

MCGUFFIN, P., ALSABBAN, S. & UHER, R. (2011). The truth about genetic variation in the serotonin transporter gene and response to stress and medication. *The British Journal of Psychiatry,* 198**,** 424-427.

MCGUFFIN, P., KATZ, R., WATKINS, S. & RUTHERFORD, J. (1996). A Hospital-Based Twin Register of the Heritability of DSM-IV Unipolar Depression. *Archives of General Psychiatry,* 53**,** 129-136.

MCKITTRICK, C., MAGARINOS, A., BLANCHARD, D., BLANCHARD, R., MCEWEN, B. & SAKI, R. (2000). Chronic social stress reduces dendritic arbors in CA3 of hippocampus and decreases binding to serotonin transporter sites. *Synapse,* 36**,** 85-94.

MCNALLY, L., BHAGWAGAR, Z. & HANNESTAD, J. (2008). Inflammation, Glutamate, and Glia in Depression: *A Literature Review*. *CNS Spectr,* 13**,** 501-510.

MEANEY, M. & SZYF, M. (2005). Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. *Dialogues Clin Neurosci,* 7**,** 103-123.

MENDLEWICZ, J., KRIWIN, P., OSWALD, P., SOUERY, D., ALBONI, S. & BRUNELLO, N. (2006). Shortened onset of action of antidepressants in major depression using acetylsalicylic acid augmentation: A pilot open-label study. *Int Clin Psychopharmacol,* 21**,** 227-231.

MENDLOVIC, S., MOZES, E., EILAT, E., DORON, A., LEREYA, J., ZAKUTH, V. & SPIRER, Z. (1999). Immune activation in non-treated suicidal major depression. *Immunol Lett, 67***,** 105-108.

MERALI, Z., BRENNAN, K., BRAU, P. & ANISMAN, H. (2003). Dissociating anorexia and anhedonia elicited by interleukin-1 beta: antidepressant and gender effects on responding for "free chow" and "earned" sucrose intake. *Psychopharmacology (Berl), 165***,** 413-418.

MILL, J., WIGG, K., BURCESCU, I., VETRO, A., KISS, E., KAPORNAI, K., TAMAS, Z., BAJI, I., GADOROS, J., KENNEDY, J., KOVACS, M., BARR, C. & DISORDERS, T. I. C. F. C.-O. M. (2009). Mutation Screen and Association Analysis of the Glucocorticoid Receptor Gene (*NR3C1*) in Childhood-Onset Mood Disorders (COMD). *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 150B***,** 866-873.

MILLER, A. H., MALETIC, V. & RAISON, C. L. (2009). Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression *Biol Psychiatry, 65***,** 732-741.

MILLER, G. E. & CHEN, E. (2010). Harsh Family Climate in Early Life Presages the Emergence of a Proinflammatory Phenotype in Adolescence. *Psychological Science, 21***,** 848-856.

MILLER, G. E. & COLE, S. W. (2012). Clustering of Depression and Inflammation in Adolescents Previously Exposed to Childhood Adversity. *Biol Psychiatry, 72***,** 34-40.

MISENER, V., GOMEZ, L., WIGG, K., LUCA, P., KING, N., KISS, E., DAROCZI, G., KAPORNAI, K., TAMAS, Z., MAYER, L., GADOROS, J., BAJI, I., KENNEDY, J., KOVACS, M., VETRO, A., BARR, C. & DISORDERS, I. C. F. C.-O. M. (2008). Cytokine Genes *TNF, IL1A, IL1B, IL6, IL1RN* and *IL10,* and Childhood-Onset Mood Disorders. *Neuropsychobiology, 58***,** 71-80.

MORALES, I., FARIAS, G. & MACCIONI, R. (2010). Neuroimmunomodulation in the pathogenesis of Alzheimer's disease. *Neuroimmunomodulation, 17***,** 202-204.

MOUSSAVI, S., CHATTERJI, S., VERDES, E., TANDON, A., PATEL, V. & USTUN, B. (2007). Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet, 370***,** 851-858.

MULLER, N., SCHWARZ, M., DEHNING, S., DOUHE, A., CEROVECKI, A., GOLDSTEIN-MULLER, B., SPELLMANN, I., HETZEL, G., MAINO, K., KLEINDIENST, N., MOLLER, H.-J., AROLT, V. & RIEDEL, M. (2006). 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. *Molecular Psychiatry, 11***,** 680-684.

NANNI & VALENTINA (2012). Childhood Maltreatment Predicts Unfavorable Course of Illness and Treatment Outcome in Depression: A Meta-Analysis. *American Journal of Psychiatry, 169***,** 141.

NEMETS, H., NEMETS, B., APTER, A., BRACHA, Z. & BELMAKER, R. (2006). Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. *Am J Psychiatry, 163***,** 1098-1100.

NEROZZI, D., SANTONI, A. & BERSANI, G. E. A. (1989). Reduced natural killer cell activity in major depression: Neuroendocrine implications. *Psychoneuroendocrinology, 14***,** 295-301.
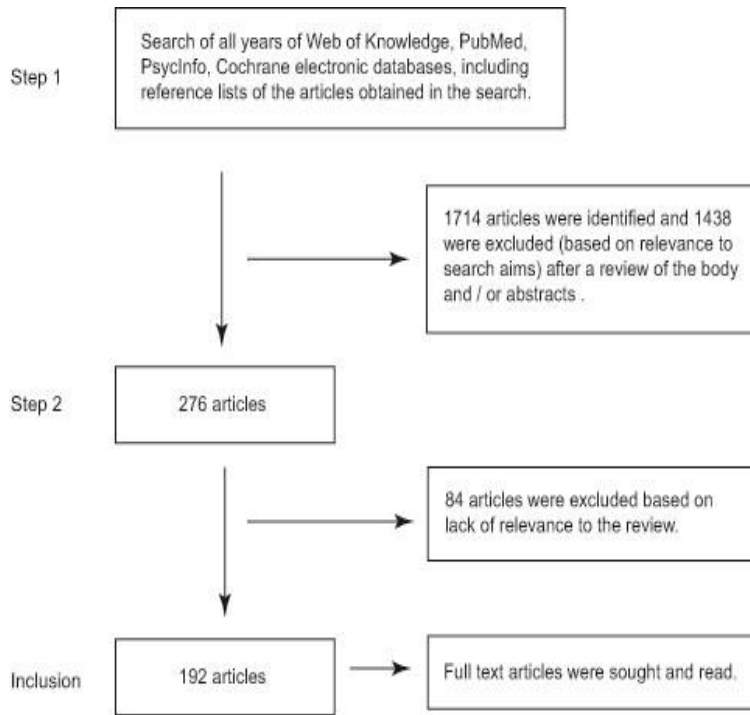
O'BRIEN, S. M., FITZGERALD, P., SCULLY, P., LANDERS, A. M., SCOTT, L. V. & DINAN, T. G. (2007a). Impact of Gender and Menstrual Cycle Phase on Plasma Cytokine Concentrations. *Neuroimmunomodulation,* 14**,** 84-90.

O'BRIEN, S. M., SCULLY, P., FITZGERALD, P., SCOTT, L. V. & DINAN, T. G. (2007b). Plasma cytokine profiles in depressed patients who fail to respond to selective serotonin reuptake inhibitor therapy. *Journal of Psychiatric Research,* 41**,** 326-331.

O'CONNOR, K., JOHNSON, J., HANSEN, M., WIESELER FRANK, J., MAKSIMOVA, E., WATKINS, L. & MAIER, S. (2003). Peripheral and central proinflammatory cytokine response to a severe acute stressor. *Brain Research,* 991**,** 123-132.

PALUCHA, A. & PILC, A. (2007). Metabotropic glutamate receptor ligands as possible anxiolytic and antidepressant drugs. *Pharmacol Ther,* 115**,** 116-147.

PANDEY, G., DWIVEDI, Y., RIZAVI, H., REN, X., PANDEY, S., PESOLD, C., ROBERTS, R., CONLEY, R. & TAMMINGA, C. (2002). Higher expression of serotonin 5-HT(2A) receptors in the postmortem brains of teenage suicide victims. *American Journal of Psychiatry,* 159**,** 419-429.

PANDEY, G. N., RIZAVI, H. S., REN, X., FAREED, J., HOPPENSTEADT, D. A., ROBERTS, R. C., CONLEY, R. R. & DWIVEDI, Y. (2012). Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. *Journal of Psychiatric Research,* 46**,** 57-63.

PAVON, L., SANDOVAL-LOPEZ, G., M, E. H., LORIA, F., ESTRADA, I., PEREZ, M., MORENO, J., AVILA, U., LEFF, P., ANTON, B. & HEINZE, G. (2006). Th2 cytokine response in Major Depressive Disorder patients before treatment. *J Neuroimmunol,* 172**,** 156-165.

PEDERSEN, B. K. (2009). Edward F Adolph distinguished lecture: muscle as an endocrine organ: IL-6 and other myokines. *J Appl Physiol,* 107**,** 1006-1014.

PENG, Y., QIU, Y., LU, J. & WANG, J. (2005). Interleukin-6 protects cultured cerebellar granule neurons against glutamate-induced neurotoxicity. *Neurosci Lett,* 374**,** 192-196.

PGC (2012). A mega-analysis of genome-wide association studies for major depressive disorder. Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium. *Molecular Psychiatry,* Apr 3 doi:10.1038/mp.2012.21**,** 1-15.

PITTENGER, C., SANACORA, G. & KRYSTAL, J. H. (2007). The NMDA Receptor as a Therapeutic Target in Major Depressive Disorder. *CNS & Neurological Disorders - Drug Targets,* 6**,** 101-115.

QIN, L., WU, X., BLOCK, M., LIU, Y., BREESE, G., HONG, J., KNAPP, D. & CREWS, F. (2007). Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *Glia,* 55**,** 453-462.

QUINONES, M. P., WILLIAMSON, D. E., LIVI, C. B., OLVERA, R. & WALSS-BASS, C. (2012). Role of the Immunomodulatory Cytokines Interferon Alpha (IFNalpha)-2 and Interleukin (IL)-10 in the Pathogenesis of Anxiety and Depression Symptoms in Adolescents: Effect of familial Risk and Stress. *Biol Psychiatry,* 71**,** 1S-316S.

RAGGI, P., SU, S., KAROHL, C., VELEDAR, E., ROJAS-CAMPOS, E. & VACCARINO, V. (2010). Heritability of Renal Function and Inflammatory Markers in Adult Male Twins. *American Journal of Nephrology,* 32**,** 317-323.

RAISON, C. L., RUTHERFORD, R. E., WOOLWINE, B. J., SHUO, C., SCHETTLER, P., DRAKE, D. F., HAROON, E. & MILLER, A. H. (2012). A Randomized Controlled Trial of the Tumor Necrosis Factor Antagonist Infliximab for Treatment-Resistant Depression:

The Role of Baseline Inflammatory Biomarkers. *Archives of General Psychiatry,* Published online Sept 3**,** E1-E11.

RANSAHOFF, R. & BENVENISTE, E. (2006). Cytokines and the CNS. New York: Taylor & Francis Group.

RISCH, N., HERRELL, R., LEHNER, T., LIANG, K., EAVES, L. & HOH, J. E. A. (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *J Am Med Assoc,* 301**,** 2462-2471.

ROSA, A., PERALTA, V., PAPIOL, S., CUESTA, M., SERRANO, F., MARTINEZ-LARREA, A. & FANANAS, L. (2004). Interleukin-1beta (IL-1beta) gene and increased risk for the depressive symptom-dimension in schizophrenia spectrum disorders. *Americal Journal of Medical Genetics. Part B, Neuropsychiatric Genetics,* 124B**,** 10-14.

ROTHERMUNDT, M., AROLT, V., FENKER, J., GUTBRODT, H., PETERS, M. & KIRCHNER, H. (2001). Different immune patterns in melancholic and non-melancholic major depression. *Eur Arch Psychiatry Clin Neurosci,* 251**,** 90-97.

ROTHWELL, N. & LODDICK, S. (2002). Immune and Inflammatory Responses in the Nervous System. New York: Oxford University Press.

RUHE, H., MASON, N. & SCHENE, A. (2007). Mood is indirectly related to serotonin, norepinephrine, and dopamine levels in humans: a meta-analysis of monoamine depletion studies. *Molecular Psychiatry,* 12**,** 331-359.

SAS, A. A., JAMSHIDI, Y., ZHENG, D., WU, T., KORF, J., ALIZADEH, B. Z., SPECTOR, T. D. & SNIEDER, H. (2012). The age-dependency of genetic and environmental influences on serum cytokine levels: A twin study. *Cytokine,* 60**,** 108-113.

SCHLEIFER, S., BARTLETT, J., KELLER, S., ECKHOLDT, H., SHIFLETT, S. & DELANEY, B. (2002). Immunity in adolescents with major depression. *Journal American Academy of Child and Adolescent Psychiatry,* 41**,** 1054-1060.

SCHLEIFER, S. J., KELLER, S. E., MEYERSON, A. T., RASKIN, M. J., DAVIS, K. L. & STEIN, M. (1984). Lymphocyte Function in Major Depressive Disorder. *Arch Gen Psychiatry,* 41**,** 484-486.

SCHWARCZ, R., WHETSELL, W. J. & MANGANO, R. (1983). Quinolinic acid: An endogenous metabolite that produces axon-sparing lesions in rat brain. *Science,* 219**,** 316-318.

SCHWARZ, E., SCHAFER, C., BODE, J. & BODE, C. (1999). Influence of the menstrual cycle on the LPS-induced cytokine response of monocytes. *Cytokine,* 12**,** 413-416.

SHAIN, B., KRONFOL, Z., NAYLOR, M., GOEL, K., EVANS, T. & SCHAEFER, S. (1991). Natural killer cell activity in adolescents with major depression. *Biol Psychiatry,* 29**,** 481-484.

SHARPLEY, C. F. & AGNEW, L. L. (2011). Cytokines and depression: findings, issues, and treatment implications. *Reviews in the Neurosciences,* 22**,** 295-302.

SLUZEWSKA, A., SOBIESKA, M. & RYBAKOWSKI, J. (1997). Changes in acute-phase proteins during lithium potentiation of antidepressants in refractory depression. *Neuropsychobiology,* 35**,** 123-127.

SMITH, R. (1991). The macrophage theory of depression. *Med. Hypotheses,* 35**,** 298-306.

SOLOMON, M., FURAY, A., JONES, K., PACKARD, A., PACKARD, B., WULSIN, A. & HERMAN, J. (2012). Deletion Of Forebrain Glucocorticoid Receptors Impairs Neuroendocrine Stress Responses And Induces Depression-like Behavior In Males But Not Females. *Neuroscience,* 203**,** 135-143.

SONG, C. (2002). The effect of thymectomy and IL-1 on memory: Implications for the relationship between immunity and depression. *Brain, Behavior, and Immunity,* 16**,** 557-568.

STEENSBERG, A., FISCHER, C. P. & AL., E. (2003). IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *Am J Physiol Endocrinol Metab,* 285**,** E433-E437.

STEPTOE, A. E. A. (2003). Lack of association between depressive symptoms and markers of immune and vascular inflammation in middle-aged men and women. *Psychol Med,* 33**,** 667-674.

SUN, X., ZHAO, Y. & WOLF, M. (2005). Dopamine receptor stimulation modulates AMPA receptor synaptic insertion in prefrontal cortex neurons. *Journal of Neuroscience,* 25**,** 7342-7351.

SUTCIGIL, L., OKTENLI, C., MUSABAK, U., BOZKURT, A., CANSEVER, A., UZUN, O., SANISOGLU, S., YESILOVA, Z., OZMENLER, N., OZSAHIN, A. & SENGUL, A. (2007). Pro- and anti-inflammatory cytokine balance in major depression: effect of sertraline therapy. *Clinical and Developmental Immunology,* 26438**,** Article No. 76396.

SZCZEPANKIEWICZ, A., LESZCZYNSKA-RODZIEWICZ, A., PAWLAK, J., RAJEWSKA-RAGER, A., DMITRZAK-WEGLARZ, M., WILKOSC, M., SKIBINSKA, M. & HAUSER, J. (2011). Glucocorticoid receptor polymorphism is associated with major depression and predominance of depression in the course of bipolar disorder. *Journal of Affective Disorders,* 134**,** 138-144.

SZELENYI, J. & VIZI, E. (2007). The catecholamine cytokine balance: interaction between the brain and the immune system. *Ann N Y Acad Sci,* 1113**,** 311-324.

TALER, M., GIL-AD, I., LOMNITSKI, L., KOROV, I., BAHARAV, E., BAR, M., ZOLOKOV, A. & WEIZMAN, A. (2007). Immunomodulatory effect of selective serotonin reuptake inhibitors (SSRIs) on human T lymphocyte function and gene expression. *European Neuropsychopharmacology,* 17**,** 774-780.

TALGE, N., NEAL, C. & GLOVER, V. (2007). Antenatal maternal stress and long-term effects on child neurodevelopment: How and why? *Journal of Child Psychology and Psychiatry,* 48**,** 245-261.

TARGUM, S. D., CLARKSON, L. L., MAGAC-HARRIS, K., MARSHALL, L. E. & SKWERER, R. G. (1990). Measurement of cortisol and lymphocyte subpopulations in depressed and conduct-disordered adolescents. *Journal of Affective Disorders,* 18**,** 91-96.

TAYLOR, S. E., LEHMAN, B. J., KIEFE, C. I. & SEEMAN, T. E. (2006). Relationship of Early Life Stress and Psychological Functioning to Adult C-Reactive Protein in the Coronary Artery Risk Development in Young Adults Study. *Biological Psychiatry,* 60**,** 819-824.

TONELLI, L. H., STILLER, J., RUJESCU, D., GIEGLING, I., SCHNEIDER, B., MAURER, K., SCHNABEL, A., MOELLER, H. J., CHEN, H. H. & POSTOLACHE, T. T. (2008). Elevated cytokine expression in the orbitofrontal cortex of victims of suicide. *Acta Psychiatrica Scandinavica,* 117**,** 198-206.

TUGLU, C., KARA, S., CALIYURT, O., VARDAR, E. & ABAY, E. (2003). Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. *Psychopharmacology (Berl),* 170**,** 429-433.

TYRING, S., GOTTLIEB, A., PAPP, K., GORDON, K., LEONARDI, C., WANG, A., LALLA, D., WOOLLEY, M., JAHREIS, A., ZITNIK, R., CELLA, D. & KRISHNAN, R. (2006). Etanercept and clinical outcomes, fatigue and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet,* 367**,** 29-35.

UDINA, M., CASTELLVI, P., MORENO-ESPANA, J., NAVINES, R., VALDES, M., FORNS, X., LANGOHR, K., SOLA, R., VIETA, E. & MARTIN-SANTOS, R. (2012). Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. *J Clin Psychiatry,* 73**,** 1128-1138.

UHER, R., CASPI, A., HOUTS, R., SUGDEN, K., WILLIAMS, B., POULTON, R. & MOFFITT, T. E. (2011). Serotonin transporter gene moderates childhood maltreatment's effects on persistent but not single-episode depression: Replications and implications for resolving inconsistent results. *Journal of Affective Disorders,* 135**,** 56-65.

USTUN, T. & CHATTERJI, S. (2001). *Global burden of depressive disorders and future projections,* London: BMJ Books.

VAN WEST, D., VAN DEN EEDE, F., DEL-FAVERO, J., SOUERY, D., NORRBACK, K. & VAN DUIJN, C. E. A. (2006). Glucocorticoid receptor gene-based SNP analysis in patients with recurrent major depression. *Neuropsychopharmacology,* 31**,** 620-627.

VERTHELYI, D. (2001). Sex hormones as immunomodulators in health and disease. *International Immunopharmacology,* 1**,** 983-993.

WATKINS, L., WIERTELAK, E., GOEHLER, L., MOONEY-HEIBERGER, K., MARTINEZ, J., FURNESS, L., SMITH, K. & MAIER, S. (1994). Neurocircuitry of illness-induced hyperalgesia. *Brain Res,* 639**,** 283-299.

WEAVER, I. C., CERVONI, N., CHAMPAGNE, F. A., D'ALESSIO, A. C., SHARMA, S., SECKL, J. R., DYMOV, S., SZYF, M. & MEANEY, M. J. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience,* 7**,** 847-854.

WEISSMAN, M., WOLK, S., GOLDSTEIN, R., MOREAU, D., ADAMS, P., GREENWALD, S., KLIER, C., RYAN, N., DAHL, R. & WICKRAMARATNE, P. (1999). Depressed adolescents grown up. *J. Am. Med. Assoc.,* 281**,** 1707-1713.

WILSON, C. J., FINCH, C. E. & COHEN, H. J. (2002). Cytokines and Cognition - The Case for A Head-to-Toe Inflammatory Paradigm. *Geriatric Bioscience,* 50**,** 2041-2056.

WOLF, M., SUN, X., MANGIAVACCHI, S. & CHAO, S. (2004). Psychomotor stimulants and neuronal plasticity. *Neuropharmacology,* 47**,** 61-79.

WORNS, M., VICTOR, A., GALLE, P. & HOHLER, T. (2006). Genetic and environmental contributions to plasma C-reactive protein and interleukin-6 levels - a study in twins. *Genes and Immunity,* 7**,** 600-605.

XIA, Z., DEPIERRE, J. & NASSBERGER, L. (1996). Tricyclic antidepressants inhibit IL-6-1 beta and TNF-alpha release in human blood monocytes and IL-2 and interferon-gamma in. *Immunopharmacology,* 34**,** 27-37.

YIRMIYA, R. (2000). Depression in medical illness: the role of the immune system. *Western Journal of Medicine,* 173**,** 333-336.

YIRMIYA, R., WEIDENFELD, J., POLLAK, Y., MORAG, M., MORAG, A., AVITSUR, R., BARAK, O., REICHENBERG, A., COHEN, E., SHAVIT, Y. & OVADIA, H. (1999). Cytokines, "depression due to a general medical condition," and antidepressant drugs. In R. DANTZER, E. E. WOLLMAN & R. YIRMIYA (Eds.) *Cytokines, Stress, and Depression.* (pp. 283-316).

ZISOOK, S., RUSH, A., ALBALA, A., ALPERT, J., BALASUBRAMANI, G., FAVA, M., HUSAIN, M., SACKEIM, H., TRIVEDI, M. & WISNIEWSKI, S. (2004). Factors that differentiate early vs. later onset of major depression disorder. *Psychiatry Res,* 129**,** 127-140.

Figure 1: Study inclusion flowchart

Step 1 → Search of all years of Web of Knowledge, PubMed, PsycInfo, Cochrane electronic databases, including reference lists of the articles obtained in the search.

→ 1714 articles were identified and 1438 were excluded (based on relevance to search aims) after a review of the body and / or abstracts .

Step 2 → 276 articles

→ 84 articles were excluded based on lack of relevance to the review.

Inclusion → 192 articles → Full text articles were sought and read.

Legend:
Inclusion criteria: Search was carried out applying the following combinations of terms – 1. Cytokines AND adolescents AND depression, 2. Cytokines AND adolescents AND cognition, 3.Cytokines AND depression AND genes, 4. Cytokines AND cognition AND genes, 5.Cytokines AND depression AND cognition, 6.Cytokines AND immun* AND depression AND stress.
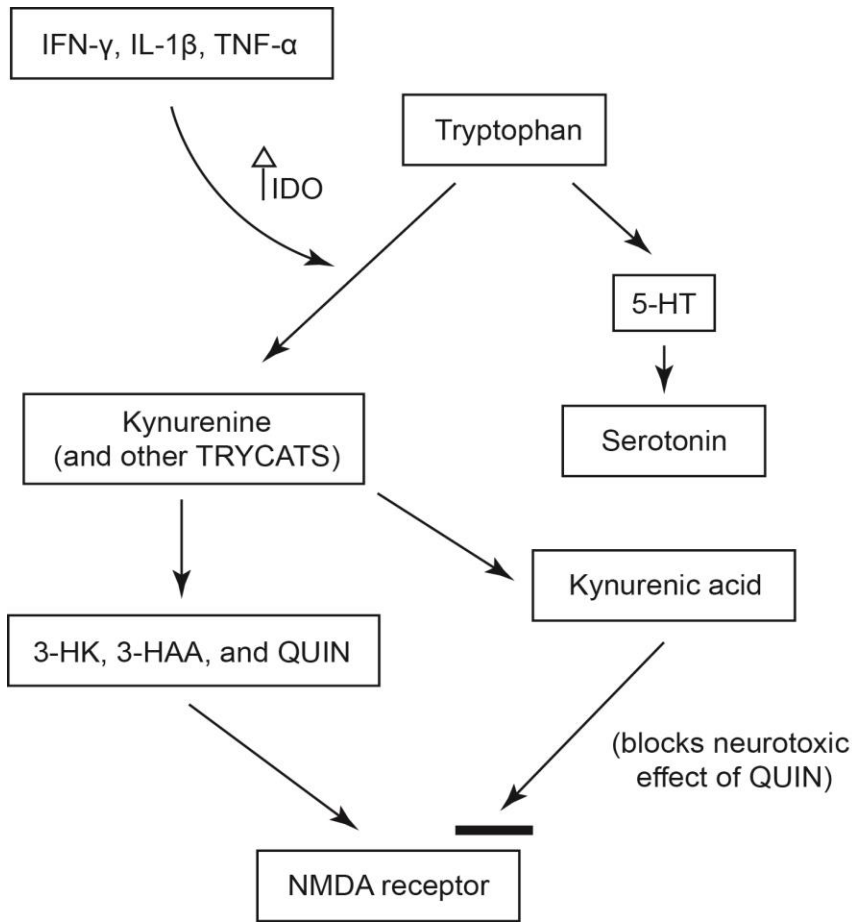Exclusion criteria: articles written in languages other than English

Figure 2 Immunological Factors involved with Depression
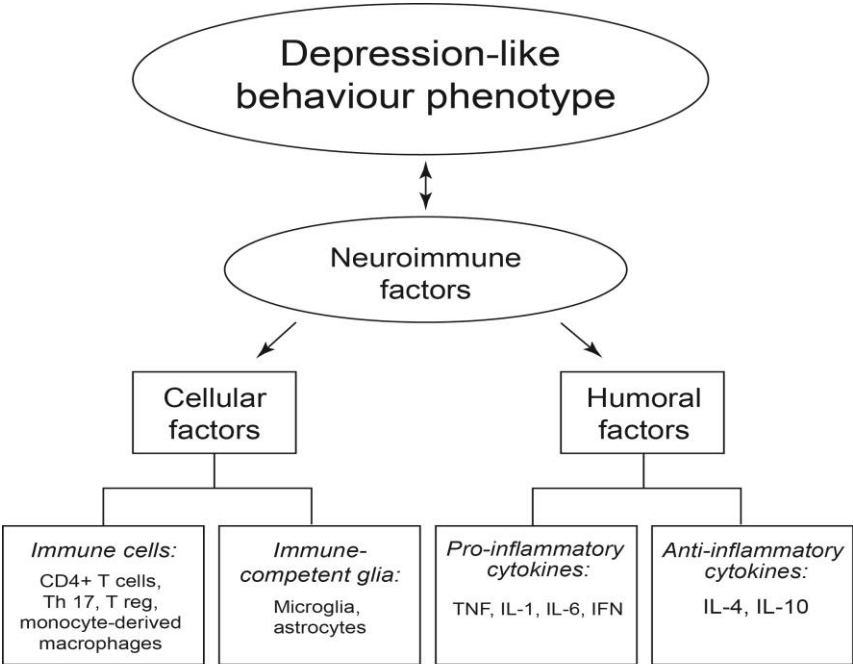
Key: IL= interleukin; IFN= interferon; NK= natural killer cells; TNF= tumor necrosis factor; Th = T

helper cell; T reg = regulatory T cells

Figure 3: Tryptophan pathways

Key: 5-HT= 5-hydroxytryptamine; HAA=hydroxyanthranilic acid; HK= hydroxykynurenine; IDO= indoleamine 2-3-dioxygenase; ↑IDO= increased levels of IDO; IFN= interferon; IL= interleukin;
NMDA= *N*-methyl-D-aspartate; QUIN= quinolinic acid; TNF= tumor necrosis factor;
TRYCATS= tryptophan catabolites along the IDO pathway

Table 1: Studies of Immune Markers in Depression in Adolescents

Study	Objectives	Design	Immune markers	Results
Targum *et al.,* 1990	Determine if hospitalized adolescents with MDD or conduct disorder (CD) show reduced lymphocyte populations compared to controls, and whether there is an association between reduced lymphocyte nos / subpopulations and cortisol dysregulation in hospitalized adolescents	30 (11 patients with MDD, ages 15.5+/-1.6 yrs; 11 with conduct disorder (CD), ages 15.3+/-1.2 yrs; 8 controls, ages 14.1+/-1.5 yrs); cross-sectional study	Total T cells, CD4+, CD8+, CD16, total B cells	No significant differences on any lymphocyte measure between patients and controls

Shain *et al.*, 1991	To compare natural killer (NK) cell activity in depressed adolescent patients with NK cell activity in age- and sex-matched controls	32 (16 patients, 16 controls), ages 13-18 yrs; cross-sectional study	NK cell activity	No significant differences between patients and matched controls. Age significantly correlated with NK cell activity.
Birmaher *et al.*, 1994	Determine whether adolescents with MDD have disturbances in their cellular immunity, and to study whether the immunological changes detected are specific to depression or are general responses to stress	54 (20 patients with MDD, 17 non-depressed patients with conduct disorder (CD), 17 healthy controls), ages 11-18 yrs, Tanner stage III	NK cell activity, lymphocyte subtypes	Patients with CD significantly higher absolute number of B cells than healthy controls (p=0.02), and a significantly greater % of B cells than MDD group (p=0.05) and controls (p=0.02). Patients with CD (who

		or more; cross-sectional study		had significantly more adverse life events) showed a trend for lower NK cell activity than those in the MDD group (p=0.08) and the control group (p=0.08).
Bartlett *et al.*, 1995	To examine for differences in immunity between children with MDD and healthy controls	36 (18 patients, 18 controls), ages 8-12 yrs; cross-sectional study	Total white blood cells (wbc), lymphocytes, T cells, B cells, monocytes, NK cells, CD4+, CD8+	Lowered NK cell activity in depressed subjects compared to healthy controls (p<0.001).

			cells	
Schleifer *et al.,* 2002	To determine if immune changes in MDD are age-related	72 (36 patients, 36 healthy controls), ages 14-20 yrs; cross-sectional study	Total wbc, lymphocytes, granulocytes, monocytes, T cells, B cells, CD4+, CD8+, CD29+, CD45RA+, NK cells, HLA-DR+ cells	Increased levels of lymphocytes, T cells, B cells, CD4+, and CD29+ lymphocytes in depressed group compared to controls ($p<.05$). Increased NK cell activity in MDD adolescents ($p< .001$)
Caserta *et al.* 2011	To test the hypothesis that self-reported efficacy and depression would predict immunity and rate of illnesses.	141 children; assessed on 3 occasions, 6 months apart;	IL-6, NK cell functional assay	Negative association between self-efficacy and IL-6 ($p=0.03$); depression was associated with

		self-efficacy measured by self-report; parents recorded illness (mental health problems were not coded as illness); longitudinal study; age 7-13 years (median age 9.3 years)		increased NK cell function (p=0.02) and higher rates of illness (p<0.01) in girls older than 9.3 years of age;

Key: CD= Conduct Disorder; CD cells= Cluster of Differentiation; MDD= Major Depressive Disorder; NK cells= natural killer cells;

wbc= white blood cells

Table 2: Clinical Studies of Cytokines / Inflammatory Markers in Depression in Adolescents

Study	Objectives	Design	Inflammatory Markers	Results
Brambilla et al., 2004	To determine whether cytokine secretion is impaired at an early phase of development of depression, possibly involvement in the course of the disease	33 (22 patients, 11 psychologically healthy controls), ages 6-14 yrs; cross-sectional study	Plasma IL-1β, TNF-α	IL-1β levels significantly higher ($p<0.0003$, $z= -2.95$) and TNF-α lower ($p<0.01$, $z= -2.53$) in dysthymic patients than in controls; IL-1β and TNF-α not significantly different between MDD and controls.
Gabbay et al., 2009a	To examine immune system dysregulation in adolescents with MDD	45 (30 patients, 15 healthy controls), ages	Plasma IFN-γ, TNF-α, IL-6, IL-1β, IL-4	Significantly increased plasma level of IFN-γ ($p<0.003$, Bonferroni

		12-19 yrs; cross-sectional study		corrected p<0.02) and IFN-γ/IL-4 ratio (p=0.007, Bonferroni corrected p<0.05) in adolescents with MDD; Trend for increased IL-6 in adolescents with MDD compared to controls (p=0.09)
Gabbay *et al.*, 2009b	To examine the role of cytokines in suicidal symptomatology in adolescent MDD	Patient group as above (30 patients – 12 suicidal, 18 non-suicidal; 15 controls);	Plasma IFN-γ, TNF-α, IL-6, IL-1β, IL-4	Suicidal adolescents had significantly decreased plasma levels of TNF-α compared to non-suicidal adolescents with MDD (p=0.03);

		cross-sectional study		Increased IFN-γ in both suicidal (p<0.02) and non-suicidal (p=0.005) adolescents with MDD compared to controls;
Gabbay *et al.*, 2010	To examine whether MDD in adolescents has distinct biological features in the kynurenine pathway in MDD case with (M-MDD) and without (Non M-MDD) melancholic features;	20 adolescents with M-MDD, 30 adolescents with non M-MDD, 22 healthy controls. Ages 12-19yrs. Cross-sectional study	Plasma TRP, KYN, 3-HAA	KYN/TRP ratios significantly elevated and TRP concentrations significantly reduced M-MDD group compared to non M-MDD adolescents (p=0.001; p=0.006 respectively), and controls (p=0.008; p=0.02 respectively);

				Significant positive correlation between 3-HAA/KYN and MDD severity in the M-MDD group (p=0.03);
Henje Blom *et al.* 2011	To study effects of antidepressants on systemic cytokines in post pubertal adolescent females with anxiety disorders and/or MDD compared to healthy controls	42 adolescent females with MDD, 60 healthy controls; age 14 – 18 years; cross-sectional study	Plasma IL-1β, IL-2, IL-6, IL-10, IFN-γ, TNF-α	Unmedicated subgroup of clinical sample showed significantly higher IL-2, IL-1β and IL-6 compared to controls (adjusted Z= -3.3, p<0.001; adjusted Z= -2.2, p<0.05; adjusted Z= -2.3, p<0.05 respectively); in the

				medicated subgroup, only IL-2 was significantly higher as compared to controls(adjusted Z= 2.3, p<0.05). Unmedicated subgroup of clinical sample showed significantly higher IL-6 and IL-6/IL-10 compared to medicated subgroup (adjusted Z= 2.8, p<0.001, adjusted Z= 2.5, p<0.05

			respectively);
Pandey *et al.* 2012	To examine the role of pro-inflammatory cytokines in suicide	24 suicide victims, 24 controls. Cause of death for the controls varied (e.g heart disease, motor vehicle accident); unclear if controls ever attempted suicide; Ages 12-20 years;	Protein and mRNA levels of TNF-α, IL-1β and IL-6 in prefrontal cortex	Significantly increased mRNA levels of TNF-α, IL-1β and IL-6 in Brodmann area 10 of the PFC in suicide victims($p<0.01$). Significantly increased protein levels of TNF-α and IL-1β in Brodman area 10 of the PFC in suicide victims ($p<0.01$)

		cross-sectional study		
Quinones et al. 2012	To further understand the role of specific immune mediators early in the development of depression and anxiety	A group at high familial risk for MDD (n=134), and an age and sex matched low-risk group (n=149); no previous mood disorder or substance abuse diagnosis. Ages 12-15 years;	Plasma cytokine levels	IL-10 was significantly associated with anxiety and depression scores; IFNα2 levels were correlated with anxiety scores independent of familial risk for mood disorders and environmental stressors

		cross-sectional study		

Key: CRP= C-reactive protein; HAA= hydroxyanthranilic acid; IFN= interferon; IL= interleukin; KYN= kynurenine;

LPS= lipopolysaccharide; MDD= Major Depressive Disorder; M-MDD= Major Depressive Disorder with melancholic features; NK cell = natural killer cell; TNF= tumor necrosis factor; TRP= tryptophan

Table 3: Population based Epidemiological Studies of Cytokines / Inflammatory Markers in Adolescents

Study	Objectives	Design	Inflammatory Markers	Results
Miller and Chen, 2010	To evaluate if a harsh environment engenders a pro-inflammatory phenotype in children that is marked by exaggerated cytokine responses to bacterial stimuli and the anti-inflammatory properties of cortisol	135 adolescent females, assessed at 4 occasions over an 18 month period (prospective study). No history of chronic medical or psychiatric disorders; Ages	Circulating serum IL-6, production of IL-6 following LPS stimulation, and resistance to glucocorticoids	Those raised in a harsh environment showed increased IL-6 response to 2 different types of threatening stimuli - in vitro LPS (p=0.01) and a stressful life event (p=0.001). Over this time, subjects also showed progressive desensitization of the glucocorticoid receptor

		15-19 yrs at time of study entry		(p=0.04)
Chaiton *et al.,* 2010	To study the association between high-sensitivity C-reactive protein concen-trations and depressive symptoms in youth	1,535 (721 aged 13 yrs, 814 aged 16 yrs); cross-sectional study	CRP	No apparent association between depressive symptoms and serum CRP (p=0.81)
Copeland *et al.*, 2012	To test 1. Effect of CRP levels on later depression status; 2. Effect of depression status on later CRP levels; 3. Effect of cumulative episodes of depression on later CRP levels	1,420 children, ages 9, 11, and 13 years at intake; longitudinal study, with annual	CRP (measured in dried blood spot samples)	CRP levels were not associated with later depression status. CRP levels increased with number of prior depressive episodes. Only cumulative

		assessments to age 16 years, and again at ages 19 and 21 years; depression assessed by a structured interview		depressive episodes predicted later CRP levels after controlling for covariates (p= 0.02)
Miller and Cole, 2012	1. To aim to clarify the direction of the association between depression and inflammation 2. To determine whether other kinds of childhood adversity (besides childhood maltreatment) also promote clustering	147 adolescent females, assessed every 6 months over 2.5 years. Ages 15-19 years at	Serum CRP, IL-6	High levels of IL-6 predicted risk of depression 6 months later in those with a history of childhood adversity (serum IL-6

		time of study entry; longitudinal study		odds ratio 1.50, 95% CI 1.10-2.06, p=0.01). Higher CRP levels remained 6 months after depressive episode had abated in those subjects exposed to higher levels of childhood adversity.
(Hood et al., 2012)	1. To provide preliminary evidence that the increased risk for depression in youth with diabetes is associated with metabolic and inflammatory markers 2. To inform future examinations of	2,359 youths with diabetes from the SEARCH study – an observational	CRP, IL-6	CRP was significantly (p<0.006) associated with depression in youth with diabetes in bivariate analysis. In regression models

	the directionality of these associations	study of US children diagnosed with diabetes at <20 years of age. Mean age of study participants 15.2 +/- 3.1 yrs		stratified by diabetes type and accounting for demographic and clinical characteristics, only higher levels of apoB remained associated with higher levels of depression in youth with type 1 diabetes.

Key: CRP= C-reactive protein; IL= interleukin; LPS= lipopolysaccharide