# A biological explanation for depression: The role of interleukin-6 in the aetiology and pathogenesis of depression and its clinical implications

**Stephy Zhang**
Fourth Year Medicine (Undergraduate)
James Cook University

*Stephy has a special interest in mental health, particularly in rural and remote Australia. She hopes to promote awareness about the importance of mental health in communities by breaking down the negative perception surrounding it. In the near future, she hopes to also conduct research in the field of mental health in Indigenous populations.*

Depression is one of the most common health problems addressed by general practitioners in Australia. It is well known that biological, psychosocial and environmental factors play a role in the aetiology of depression. Research into the possible biological mechanisms of depression has identified interleukin-6 (IL-6) as a potential biological correlate of depressive behaviour, with proposed contributions to the aetiology and pathogenesis of depression. Interleukin-6 is a key proinflammatory cytokine involved in the acute phase of the immune response and a potent activator of the hypothalamic-pitutary-adrenal axis. Patients with depression have higher than average concentrations of IL-6 compared to non-depressed controls, and a dose-response correlation may exist between circulating IL-6 concentration and the degree of depressive symptoms. Based on these insights the 'cytokine theory of depression' proposes that proinflammatory cytokines, such as IL-6, act as neuromodulators and may mediate some of the behavioural and neurochemical features of depression. Longitudinal and case-control studies across a wide variety of patient cohorts, disease states and clinical settings provide evidence for a bidirectional relationship between IL-6 and depression. Thus IL-6 represents a potential biological intermediary and therapeutic target for the treatment of depression. Recognition of the strong biological contribution to the aetiology and pathogenesis of depression may help doctors to identify individuals at risk and implement appropriate measures, which could improve the patient's quality of life and reduce disease burden.

## Introduction

Our understanding of the immune system has grown exponentially within the last century, and more questions are raised with each new development. Over the past few decades research has emerged to suggest that the immune system may be responsible for more than just fighting everyday pathogens. The term 'psychoneuroimmunology'was first coined by Dr Robert Ader and his colleagues in 1975 as a conceptual framework to encompass the emerging interactions between the immune system, the nervous system, and psychological functioning. Cytokines have since been found to be important mediators of this relationship. [1] There is considerable research that supports the hypothesis of proinflammatory cytokines, in particular interleukin-6 (IL-6), in playing a key role in the aetiology and pathophysiology of depression. [1-5] While both positive and negative results have been reported in individual studies, a recent meta-analysis supports the association between depression and circulating IL-6 concentration. [6] This review will explore the impact of depression in Australia, the role of IL-6 and the proposed links to depression and clinical implications of these findings.

## Depression in Australia and its diagnosis

Depression belongs to a group of affective disorders and is one of the most prevalent mental illnesses in Australia. [7] It contributes to one of the highest disease burdens in Australia, closely following cancers and cardiovascular diseases. [7] Most of the burden of mental illness, measured as disability adjusted life years (DALYs), is due to years of life lost through disability (YLD) as opposed to years of life lost to death (YLL). This makes mental disorders the leading contributor (23%) to the non-fatal burden of disease in Australia. [7] Specific populations, including patients with chronic disease, such as diabetes, cancer,

cardiovascular disease, and end-stage kidney disease, [1,3,4,10] are particularly vulnerable to this form of mental illness.[8, 9] The accurate diagnosis of depression in these patients can be difficult due to the overlapping of symptoms inherent to the disease or treatment and the diagnostic criteria for major depression. [10-12] Nevertheless, accurate diagnosis and treatment of depression is essential and can result in real gains in quality of life for patients with otherwise incurable and progressive disease. [7] Recognising the high prevalence and potential biological underpinnings of depression in patients with chronic disease is an important step in deciding upon appropriate diagnosis and treatment strategies.

## Role of IL-6 in the body

Cytokines are intercellular signalling polypeptides produced by activated cells of the immune system. Their main function is to coordinate immune responses; however, they also play a key role in providing information regarding immune activity to the brain and neuroendocrine system. [13] Interleukin-6 is a proinflammatory cytokine primarily secreted by macrophages in response to pathogens. [14] Along with interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α), IL-6 plays a major role in fever induction and initiation of the acute-phase response. [14] The latter response involves a shift in the composition and abundance of proteins synthesised and secreted by the liver, favouring several acute phase proteins that act like broad spectrum antibodies to opsonise pathogens and activate complement cascade. [14] Some examples of these include C-reactive protein (CRP), mannan-binding lectin and serum amyloid protein. [14] Interleukin-6 also regulates T-cell activation and proliferation, B cell growth and differentiation, antibody production and prostaglandin secretion. [15]

Numerous studies in human and animal models have shown that inflammatory cytokines can induce 'sickness behaviour.' Sickness behaviour consists of a group of symptoms including fatigue, anorexia, anhedonia, psychomotor retardation, altered sleep patterns, defects in learning and memory and reduction of personal hygiene and grooming. [16] The signs and symptoms that accompany immunologic responses to infection overlap significantly with the symptoms seen in the development and maintenance of depression. [11,17,18] Of the numerous cytokines secreted in the inflammatory response, IL-6 has shown a particularly robust association with depressive symptoms. [6] Numerous studies have documented higher than normal plasma concentrations of IL-6 in depressed individuals compared to non-

depressed, healthy controls. [1-4,9,11,18] This positive association has been consistently demonstrated in both clinical and community based trials. As a result of this, special attention has been placed on the role of IL-6 in the aetiology and pathogenesis of depression.

## Proposed links between IL-6 and depression

The 'cytokine theory of depression' proposes that proinflammatory cytokines such as IL-6 act as neuromodulators and may mediate some of the behavioural and neurochemical features of depression. [4] In addition to depressed individuals possessing higher than average concentrations of IL-6, [6] it has been suggested that a dose-response relationship may exist between IL-6 concentration and the severity of depressive symptoms. [11,18] Higher concentrations of cytokines may therefore induce greater degrees of 'sickness behaviour.' Furthermore, Maes *et al.* [5] reported that plasma concentrations of soluble IL-6 receptor (sIL-6R) were significantly increased in patients with major depression. They proposed that the positive relationship between IL-6 and sIL-6R concentrations may be due to the hyperproduction of IL-6, causing an upregulation of the expression of IL-6 receptor mRNA. This simultaneous upregulation of IL-6 and sIL-6R in the plasma of patients with major depression may have a synergistic effect on the biological activities of IL-6. From these findings, the study hypothesised that IL-6 may elicit a greater biological response in depressed subjects than estimated from the plasma IL-6 values alone. [5]

An early study by Dentino *et al.* [17] postulated that the pathophysiologic mechanism between the observed 'sickness behaviour' and IL-6 levels was due to an immunoendocrine dysregulation. Interleukin-6 is a potent activator of all three of the organs in the hypothalamic-pituitary-adrenal axis and thus may independently stimulate an increased production of cortisol.[10,11,15,19] Sustained elevation in circulating IL-6 eventually leads to chronic pathologic hyperactivity of the HPA axis. [20] Furthermore, inflammation is possibly not the only initiator of IL-6 secretion. [21] Interleukin-6 production can also be stimulated by catecholamines in a time-dose dependent manner. [21] This suggests that strong emotional stress could induce elevated levels of plasma IL-6 independent of any inflammatory process. The hypothesis of HPA axis dysregulation has been supported in more recent studies and remains one of the key explanations for the link between IL-6 and depression. [10,15,17,20] The mechanism by which IL-6 can activate the HPA axis is not fully understood. However, some studies have reported that elevated concentrations of IL-6 induce a state of impaired glucocorticoid-mediated negative feedback on the HPA axis via inhibition of the glucocorticoid receptor. [10,22] This results in HPA hyperactivation.[10,22] In support of this concept, many observational studies have noted a decrease in the relative diurnal variation of plasma cortisol as well as reduced suppression of cortisol values post dexamethasone administration in depressed patients compared with healthy control subjects. [4,10,11,15]

While intriguing and consistent across many studies in a variety of settings, it should be recognised that associations between IL-6 concentrations and depression have not been observed in every published report. Brambilla *et al.* [23] compared IL-6 plasma concentrations in ten elderly women with major depressive disorder with ten age-matched healthy females and found no significant differences. Similar findings were reported in a study conducted by Kagaya *et al.* [24] which compared depressed patients in Japan with control subjects. Furthermore, the relationship and extent of IL-6 involvement in the clinical manifestations of different types of depression is yet to be determined. Therefore a generalised pattern between IL-6 concentrations and depressive symptoms still needs to be fully defined. [6] Alternative explanations for the relationship between IL-6 and depressive symptoms include the potential confounding effect of IL-6 as a generic marker of the acute phase response. Many other inflammatory cytokines, including IL-1, TNF-α, interleukin-2 (IL-2) and interferon-gamma have shown similar associations with depression. [4,15] Müller *et al.* [25] recently reported that IL-2, interferon-gamma and TNF-α activate the tryptophan and serotonin degrading enzyme, indoleamine 2,3-dioxygenase, leading to a reduction in tryptophan and serotonin levels. Decreased serotonin concentrations have been robustly linked to the development of depressive symptoms and pharmacotherapies aimed at enhancing serotonin signalling are the mainstay of current treatment regimes for depression. [26] Although a number of studies have shown that proinflammatory cytokines, such as IL-1, IL-2 and interferon-gamma, may contribute to the development of depressive symptoms, a recent meta-analysis reported that these associations were not significant. [6] However, the consistency and nature of the relationship between IL-6, depression and the severity of depressive symptoms has lead many experts to believe that IL-6 may have a causative role in the aetiology and pathogenesis of depression. [19] Other proinflammatory cytokines have not been shown to have the same potent effect that IL-6 exerts on the HPA axis. [11,15] Given that HPA dysfunction is hypothesised as one of the main drivers of depression symptoms, it can be inferred that IL-6 plays a notable role in the onset and progression of depression. Interestingly, there have also been recent reports that suggest a similar association between circulating IL-6 levels and patients with schizophrenia. [27]

### *Causal Pathways*

The cause-effect relationship between inflammation and depression has been researched extensively. The literature strongly suggests that a complex, bidirectional process exists between depression and inflammation. [28] It is likely that these two processes are part of a complex feedback loop that involves the neuroendocrine and immune systems. A major, long-term prospective cohort study conducted by Stewart *et al.* [29] found that the level of depressive symptoms was a predictor of six year change in IL-6, thus implying that depression may lead to inflammation. In 2001 Musselman *et al.* [3] posed that, if proinflammatory cytokines like IL-6 were to play a direct role in inducing major depression, then patients with diseases associated with immune activation may be at increased risk for depression. [3] It has since been shown that rheumatoid arthritis, Alzheimer's disease, cancer and coronary artery disease are all associated with an increase in the concentration of inflammatory markers and possess a clear association with depression. [30-32] These findings imply that immune activation due to a biological disorder may precipitate, or aggravate, depression-like symptoms. [8, 9] While those longitudinal studies that do exist [9, 29] support the bidirectional nature of the relationship between IL-6 and depression, it should be noted that most of the studies investigating the relationship between IL-6, depression and chronic disease are cross-sectional and thus cause and effect relationships cannot be directly inferred. [11] Further elucidation of the causal pathways between depression and inflammatory cytokines will require more prospective studies to be carried out in community based and clinical samples. [18]

## Clinical implications

The association between depression and circulating IL-6 concentration is supported by a large number of longitudinal and case-control studies across a wide range of patient cohorts, disease states, and clinical settings. [1,5,6, 11,17,18] This has many implications for the health of individuals with depression. Interleukin-6 stimulates CRP production, which influences the initiation and progression of atherosclerosis [33] and may also promote growth of certain types of cancer by inhibiting apoptosis and facilitating angiogenesis in solid tumours.[34, 35] Therefore, a plausible link between depression and an increased risk of cardiovascular diseases and cancer must be considered, especially in patients with other comorbidities. Our understanding of the role of IL-6 in depression also opens many avenues for novel antidepressant therapies. Inflammatory cytokine synthesis inhibitors (for example, pyridinyl imidazole compounds), cytokine antagonists and anti-inflammatory cytokines may be incorporated into the management of mood disorders. [16,36,37] One day patients may receive immunotherapy to reduce or eliminate the cytokine-induced 'sickness

behaviours.' [36] Educating the community about these findings may help alleviate the negative stigma that commonly surrounds mental health disorders. [38] This could increase the likelihood for presentation to doctors, which means an earlier diagnosis can be made and appropriate treatment plans implemented to maximise the quality of life for individuals with depression. [38]

## Conclusion

The importance of IL-6 in the aetiology and progression of depression has been implied in a number of studies. The level of IL-6 in the blood appears to be correlated with the degree of depressive symptoms. Dysregulation of the HPA axis has been strongly implicated as the major biological mechanism behind this link. A better understanding of IL-6 may lead to the development of innovative anticytokine antidepressant therapies, which could fundamentally change the way depression is perceived and treated.

## Conflict of interest

None declared.

## Correspondence

S Zhang: xirui.zhang@my.jcu.edu.au

## References

[1] Jacobson CM, Rosenfeld B, Pessin H, Breitbart W. Depression and IL-6 blood plasma concentrations in advanced cancer patients. Psychosomatics. 2008;49(1):64-6.
[2] Bob P, Roboch J, Maes M, Susta M, Pavlat J, Josova D, *et al.*, Depression, traumatic stress and interleukin-6. J Affect Disord. 2010;120(1-3):231-234.
[3] Musselman DL, Miller AH, Porter MR, Manatunga A, Gao F, Penna S, *et al.* Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: Preliminary findings. Am J Psychiatry. 2001;158(8):1252–7.
[4] Sonikian M, Metaxaki P, Papavasileiou D, Boufidou F, Nikolaou C, Vlassopoulos D, *et al.* Effects of interleukin-6 on depression risk in dialysis patients. Am J Nephrol. 2010;31(4): 303-8.
[5] Maes M, Meltzer HY, Bosmans E, Bergmans R, Vandoolaeghe E, Ranjan R, *et al.* Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2, and transferrin receptor in major depression. J Affect Disord. 1995;34(4):301-9.
[6] Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, *et al.* A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010;67(5):446-57.
[7] Australian Institute of Health and Welfare. Australia's health 2008: 11th biennial report of the Australian Institute of Health and Welfare. Canberra: AIHW; 2008. AIHW cat. no. AUS 99.
[8] Dantzer R, Kelley K. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun. 2007;21(2):153–60.
[9] Gimeno D, Kivimaki M, Brunner EJ, Elovainio M, Vogli R, Steptoe A, *et al.* Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. Psychol Med. 2009;39(3):413-23.
[10]Jehn CF, Kuhnhardt D, Bartholomae A, Pfeiffer S, Krebs M, Regierer AC, *et al.* Biomarkers of depression in cancer patients. Cancer. 2006;107(11):2723-9.
[11] Jehn CF, Kuhnhardt D, Bartholomae A, Pfeiffer S, Schmid P, Possinger K, *et al.* Association of IL-6, hypothalamus-pituitary-adrenal axis function, and depression in patients with cancer. Integr Cancer Ther. 2010. 9(3):270-5.
[12] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association. 1994.
[13] Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Psychoneuroimmunology: Psychological influences on immune function and health. J Consult Clin Psychol. 2002;70(3):537-47.
[14] Janeway CA, Travers P, Walport M. Immunobiology. 6th ed. USA: Garland Science Publishing; 2005. 85-8.
[15] Maes M, Scharpe S, Meltzer HY, Bosmans E, Suy E, Calabrese J, *et al.* Relationships between interleukin-6 activity, acute phase proteins and function of the hypothalamic-pituitary-adrenal axis in severe depression. Psychiat Res. 1993;49(1):11-27.
[16] Leonard BE, Song C. Changes in the immune system in rodent models of depression. Int J Neuropsychopharmacol. 2002;5(4):345-56.
[17] Dentino AN, Pieper CF, Rao MK, Currie MS, Harris T, Blazer DG, *et al.* Association of interleukin-6 and other biologic variables with depression in older people living in the community. J Am Geriatr Soc. 1999;47(1):6-11.
[18] Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med. 2009;71(2):171-186.
[19] Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokines. 1997;9(11):853– 8.
[20] Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med. 1996;332(20):1351-62.
[21] Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey W, *et al.* Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proceedings of the National Academy of Sciences USA. 2003;100(15):9090-5.
[22] Miller AH, Pariante CM, Pearce BD. Effects of cytokines on glucocorticoid receptor expression and function. Glucocorticoid resistance and relevance to depression. Adv Exp Med Biol. 1999;461:107-16.
[23] Brambilla F, Maggioni M. Blood levels of cytokines in elderly patients with major depressive disorder. Acta Psychiatr Scand. 1998;97(4):309-13.
[24] Kagaya A, Kugaya A, Takebayashi M, Fukue-Saeki M, Saeki T, Yamawaki S, *et al.* Plasma concentrations of interleukin-1 beta, interleukin-6, soluble interleukin-2 and tumor necrosis factor alpha of depressed patients in Japan. Neuropsychobiology. 2001;43(2):59-62.
[25] Müller N, Schwarz MJ. The immune-mediated alteration of serotonin and glutamate: Towards an integrated view of depression. Mol Psychiatry. 2007;12(11):988-1000.
[26] Rang HP, Dale MM, Ritter JM, Flower RJ. Rang and Dale's psharmacology. 6th ed. London: Elsevier; 2007. 560-8.
[27] Frommberger UH, Bauer J, Haselbauer P, Fraulin A, Riemann D, Berger M. Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: Comparison between the acute state and after remission. Eur Arch Psychiatr Clin Neurosci. 1997;247(4):228-233.
[28] Massay B, Lim A, Marsland AL. Current understanding of the bi-directional relationship of major depression with inflammation. Biol Mood Anxiety Disord. 2012;2:4.
[29] Stewart JC, Rand KL, Muldoon MF, Kamarck TW. A prospective evaluation of the depression-inflammation relationship: Is depression a cause or a consequence? 66th Annual Scientific Meeting of the American Psychosomatic Society. 2008, Baltimore, MD.
[30] Dickens C, McGowan L, Clark-Carter D, Creed F. Depression in rheumatoid arthritis: Asystemic review of the literature with meta-analysis. Psychosom Med 2002;64(1):52-60.
[31] Zorilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, *et al.* The relationship of depression and stressors to immunological assays: A meta-analytic review. Brain Behav Immun. 2001;15(3):199-226.
[32] Lesperance F, Frasure-Smith N. Depression in patients with cardiac disease: A practical review. J Psychosom Res. 2000;48(4-5):379-91.
[33] Paul A, Ko KW, Li L, Yechoor V, McCrory MA, Szalai AJ, *et al.* C-reactive protein accelerates the progression of atherosclerosis in apolipoprotein E-deficient mice. Circulation. 2004;109(18):647–55.
[34] Hodge DR, Hurt EM, Farrar WL. The role of IL-6 and STAT3 in inflammation and cancer. Eur J Cancer. 2005;41(16):2502–12.
[35] Nilsson MB, Langley RR, Fidler IJ. Interleukin-6, secreted by human ovarian carcinoma cells, is a potent proangiogenic cytokine. Cancer Res. 2005;65(23):10794–800.
[36] Maes M, Yirmyia R, Noraberg J, Brene S, Hibbeln J, Perini G, *et al.* The inflammatory & neurodegenerative (I&ND) hypothesis of depression: Leads for future research and new drug developments in depression. Metab Brain Dis. 200924(1):27–53.
[37] Schiepers OJ, Wichers MC, Maes M. Cytokines and major depression. Prog Neuro-psychopharmacol Biol Psychiatry. 2005;29(2):201-17.
[38] Barney LJ, Griffins KM, Jorm AF, Christensen H. Stigma about depression and its impact on help-seeking intentions. Aust NZ J Psychiat. 2006;40(1):51-4.