DOCUMENT SUMMARY This 2008 review paper by Robert Dantzer and colleagues explores the mechanisms by which the immune system influences the brain to cause **sickness behaviour** and, in vulnerable individuals, major **depression**. It posits that **pro-inflammatory cytokines** (like **IL-1β**, **TNF-α**, and **IL-6**), produced during infection or chronic illness, act on the brain through various pathways, leading to symptoms like fatigue, anhedonia, and social withdrawal. The paper argues that when this immune activation is prolonged or exaggerated, it can trigger depressive episodes, partly through the activation of the enzyme **indoleamine 2,3-dioxygenase (IDO)**, which depletes **tryptophan** (a precursor to serotonin) and produces neuroactive metabolites.

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FORMATTED CONTENT

From inflammation to sickness and depression: when the immune system subjugates the brain

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Abstract

In response to a peripheral infection, innate immune cells produce **pro-inflammatory cytokines** that act on the brain to cause **sickness behaviour**. When activation of the peripheral immune system continues unabated, such as during systemic infections, cancer or autoimmune diseases, the ensuing immune signalling to the brain can lead to an exacerbation of sickness and the development of symptoms of **depression** in vulnerable individuals. These phenomena might account for the increased prevalence of clinical **depression** in physically ill people.

> **Inflammation** is therefore an important biological event that might increase the risk of major depressive episodes, much like the more traditional psychosocial factors.

Anyone who has experienced a viral or bacterial infection knows what it means to feel sick. The behaviour of sick people changes dramatically; they often feel feverish and nauseated, ignore food and beverages, and lose interest in their physical and social environments. They tire easily and their sleep is often fragmented. In addition, they feel depressed and irritable, and can experience mild cognitive disorders ranging from impaired attention to difficulties in

remembering recent events. Despite their negative impact on well-being, these symptoms of sickness are usually ignored. They are viewed as uncomfortable but banal components of infections[1].

Sickness is a normal response to infection, just as fear is normal in the face of a predator. It is characterized by endocrine, autonomic and behavioural changes and is triggered by soluble mediators that are produced at the site of infection by activated accessory immune cells. These mediators are known as **pro-inflammatory cytokines**, and include interleukin-la and ß (**IL-1α** and **IL-1β**), tumour necrosis factor-a (**TNF-α**) and interleukin-6 (**IL-6**). They coordinate the local and systemic inflammatory response to microbial pathogens. However, these peripherally produced cytokines also act on the brain to cause the aforementioned behavioural symptoms of sickness.

Recently, it has been suggested that '**sickness behaviour**'[2,3], a term used to describe the drastic changes in subjective experience and behaviour that occur in physically ill patients and animals, is an expression of a previously unrecognized motivational state. It is responsible for re-organizing perceptions and actions to enable ill individuals to cope better with an infection[4].

During the last five years, it has been established that **pro-inflammatory cytokines** induce not only symptoms of sickness, but also true major depressive disorders in physically ill patients with no previous history of mental disorders. Some of the mechanisms that might be responsible for **inflammation**-mediated sickness and **depression** have now been elucidated. These findings suggest that the brain-cytokine system, which is in essence a diffuse system, is the unsuspected conductor of the ensemble of neuronal circuits and neurotransmitters that organize physiological and pathological behaviour. In this Review we discuss how the brain engenders **sickness behaviour** in response to peripheral infections. We then review the evidence that **pro-inflammatory cytokines** can also trigger the development of **depression** in vulnerable individuals, and the possible underlying mechanisms. Finally, we discuss how these actions of cytokines in the brain might have a role in at least part of the increased prevalence of **depression** in people with physical illness[5].

Immune signals from periphery to brain

The brain monitors peripheral innate immune responses by several means that act in parallel (FIG. 1).

1. **Afferent nerves:** Locally produced cytokines activate primary afferent nerves, such as the vagal nerves during abdominal and visceral infections[8–9] and the trigeminal nerves during oro-lingual infections [10].
2. **Humoral pathway:** Toll-like receptors (TLRs) on macrophage-like cells residing in the circumventricular organs and the choroid plexus respond to circulating pathogen-associated molecular patterns by producing **pro-inflammatory cytokines**[11]. As the circumventricular organs lie outside the blood-brain barrier, these cytokines can enter the brain by volume diffusion [12].
3. **Cytokine transporters: Pro-inflammatory cytokines** overflowing in the systemic circulation can gain access to the brain through these saturable transport systems[13].
4. **Perivascular IL-1 receptors:** Activation of IL-1 receptors on perivascular macrophages and endothelial cells of brain venules by circulating cytokines results in the local production of prostaglandin E2[14,15].

Engagement of these **immune-to-brain communication** pathways ultimately leads to the production of **pro-inflammatory cytokines** by microglial cells. This way the brain forms an 'image' of the peripheral innate immune response that is similar in its elementary molecular components to the response in the periphery.

Cytokines and sickness behaviour

The main **pro-inflammatory cytokines** involved in **sickness behaviour** are **IL-1β** and **TNF-α**. Systemic or central administration of **IL-1β** or **TNF-α** to rats and mice induces the full spectrum of behavioural signs of sickness in a dose- and time-dependent manner. Specifically, they show decreased motor activity, social withdrawal, reduced food and water intake, increased slow-wave sleep and altered cognition (FIG. 2).

In contrast to **IL-1β** and **TNF-α**, **IL-6** administered systemically or centrally has no behavioural effect despite its ability to induce a fever response. However, LPS-induced **sickness behaviour** and hippocampus-mediated cognitive impairment are less noticeable in **IL-6**-deficient mice than in wild-type controls[29], indicating that brain **IL-6** contributes to the expression of brain cytokines in response to immune stimuli.

Anti-inflammatory cytokines regulate the intensity and duration of **sickness behaviour**, probably by inhibiting **pro-inflammatory cytokine** production and attenuating **pro-inflammatory cytokine** signalling [30],[31]. These data are consistent with the idea that 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.

A role for cytokines in depression?

> The similarity between the symptoms of cytokine-induced **sickness behaviour** and **depression** is striking: in both cases there is a withdrawal from the physical and social environment that is accompanied by pain, malaise and decreased reactivity to reward (anhedonia).

Moreover, some components of **sickness behaviour**, such as a decreased preference for sweet solutions and reduced social exploration, are improved by anti-depressant treatment[40]. In humans, major depressive disorders develop in roughly a third of patients who are treated with the recombinant human cytokines IL-2 and interferon-a (IFN-α)[41].

> It is possible that **depression** represents a maladaptive version of cytokine-induced sickness, which could occur when activation of the innate immune response is exacerbated in intensity and/or duration, or that takes place in the context of an increased vulnerability to **depression**, for example, in individuals with hyperactive corticotrophin-releasing factor (CRH) neuronal circuits[42].

A role for cytokines in **depression** was first proposed by Smith[43] in the form of the 'macrophage theory of **depression**' and further studied by Maes in the early 1990s.

Vegetative, somatic and psychological symptoms of depression

Systematic investigation of the symptoms that developed in cancer and hepatitis C patients receiving immunotherapy confirmed that they were caused by the treatment, and revealed that they fell into two distinct categories:

- **Early-onset neurovegetative and somatic symptoms of depression**, which all patients display and which include flu-like symptoms, fatigue, anorexia, pain and sleep disorders.
- **Late-onset psychological symptoms of depression** that are experienced by up to half of patients and include mild cognitive alterations and symptoms of depressed mood, sometimes accompanied by anxiety and irritability [48–50].

Pre-treatment with paroxetine, a serotonin-reuptake inhibitor, reduces the psychological symptoms but has little or no effect on the concomitant neurovegetative symptomatology[48].

A role for tryptophan?

Immunotherapy alters the clinical biochemistry of patients; the most revealing sign is a pronounced reduction in plasma levels of **tryptophan**[56], which correlates with the patients' **depression** scores 3 weeks into the treatment. **Tryptophan** is an essential amino acid that is actively transported into the brain for the synthesis of serotonin.

The fall in plasma levels of **tryptophan** that occurs in patients receiving immunotherapy could be due to activation of the major enzymes that metabolize **tryptophan**, namely **tryptophan** 2,3 dioxygenase (TDO) and **indoleamine 2,3 dioxygenase (IDO)**. Both enzymes degrade **tryptophan** along the **kynurenine pathway** (BOX 1). **IDO** can be directly activated by a number of cytokines, including IFN-γ and **TNF-α**.

Box 1: IDO degrades tryptophan through the kynurenine pathway

Tryptophan is an essential amino acid that is required for protein synthesis and serves as a precursor for serotonin. Normally, the majority of dietary **tryptophan** (>95%) is oxydatively degraded in the liver through the **kynurenine pathway**. **Tryptophan** oxidation can also occur extrahepatically by the enzyme **indoleamine 2,3 dioxygenase (IDO)**. Although **tryptophan** degradation by **IDO** is normally negligible, **IDO** is highly inducible by **pro-inflammatory cytokines**.

Decreased **tryptophan** concentrations have the potential to influence serotonergic neurotransmission in the brain. In addition, **IDO** is expressed in the brain so that fluctuations in its enzymatic activity can affect serotonin biosynthesis. The major metabolite of **tryptophan**, kynurenine, is readily transported across the blood-brain-barrier into the brain where it can be further metabolized... to generate neuroactive compounds. Kynurenine is degraded along one of two catabolic branches, leading to the formation of either 3-hydroxykynurenine (3-HK) and quinolinic acid (QA) or kynurenic acid (KA). 3-HK generates free-radical species... whereas QA is an N-methyl-D-aspartate (NMDA) receptor agonist. By contrast, KA is an NMDA receptor antagonist...

Despite its dramatic effects on circulating levels of **tryptophan**, activation of **IDO** by cytokines does not necessarily induce depression-like behaviour through alterations in the metabolism of serotonin.

> An alternative explanation for the involvement of **IDO** in the pathophysiology of depression-like behaviour is that degradation of **tryptophan** along the **kynurenine pathway** generates compounds that act as either agonists (for example, quinolinic acid and 3 hydroxy-kynurenine) or antagonists (for example, kynurenic acid) of the NMDA (N-methyl-D-aspartate) receptor (BOX 1).

The net result is probably an alteration in glutamatergic neurotransmission that could trigger the necessary conditions for the development of **depression**[61].

Alternative mechanisms for cytokine-induced depression

Non-serotonergic mechanisms might also be involved. A hyperactive hypothalamus-pituitary-adrenal axis is often associated with clinical **depression** [65]. **Pro-inflammatory cytokines** acutely and potently activate this axis, which can be attributed to increased production of CRH[66]. In conditions of chronic **inflammation**, **pro-inflammatory cytokines** can cause glucocorticoid receptor resistance in immunocytes and their cellular targets. At the hypothalamic level, this cytokine-dependent glucocorticoid receptor resistance can explain the reduced ability of glucocorticoids to down-regulate the production of CRH.

Implications for depression in medically ill people

A growing amount of clinical data point to the importance of the relationship between **inflammation** and **depression** in physically ill patients and in conditions that are associated with increased activity of the innate immune system, including ageing and obesity. Depression has long been known to be a risk factor for subsequent cardiac events and mortality, which is usually explained by the detrimental effects of **depression** on illness behaviour including adherence to treatment.

> However, this traditional view of the relationship between **inflammation** and morbidity/mortality in physically ill patients is challenged by the new hypothesis, set out in this Review, that **depression** can actually be caused by **inflammation** in vulnerable patients[41] (FIG. 4).

Future directions

The findings described here indicate that we are starting to understand why we feel sick and behave accordingly when we are ill.

> We now also recognize that **inflammation** is an important biological event that increases the risk of occurrence of major depressive episodes, much like the more traditional psychosocial factors such as the death of a loved one.

Importantly, the rapid increase in knowledge about **immune-to-brain communication** must be translated into clinical practice. If confirmed in the clinic, the efficacy of compounds targeting **IDO** and inflammatory mediators for the alleviation of symptoms of **depression** will open new opportunities for drug development.

Figure Captions

- **Figure 1. Pathways that transduce immune signals from the periphery to the brain:** This figure illustrates the neural pathway (vagal nerve activation) and the humoral pathway (action on circumventricular organs) through which peripheral immune signals like cytokines reach the brain.
- **Figure 2. Increased brain cytokine signalling impairs learning and memory:** This figure shows how **inflammation** and the resulting interoceptive signals of sickness can increase the cognitive load on working memory, impairing hippocampal-dependent memory tasks like contextual fear conditioning.
- **Figure 3. LPS-increased depression-like behaviour in mice:** This figure illustrates the time course where peripherally administered LPS first induces **sickness behaviour** (peaking at 2-6 hours), followed by the emergence of **depression-like behaviour** (at 24 hours). This depression-like behavior is linked to the activation of **IDO**, which can be blocked by an **IDO** inhibitor (1-MT) without altering the initial **sickness behaviour**.
- **Figure 4. Depression as a consequence of decompensation of the mechanisms that regulate sickness:** This figure proposes a model where **depression** can develop on a background of sickness. This decompensation can occur in vulnerable patients with a more intense inflammatory response or a higher brain sensitivity to immune events.

Glossary

- **Accessory immune cells**: Cells such as macrophages and dendritic cells that are required for, but do not actually mediate, adaptive immune responses of T and B lymphocytes.
- **Sickness behaviour**: A motivational state that re-organizes perception and action in ill individuals, characterized by symptoms like fatigue, anorexia, and social withdrawal, induced by **pro-inflammatory cytokines**.
- **Inflammation**: A response of tissues to injury or irritation that is characterized by pain, swelling, redness and heat.
- **Pro-inflammatory cytokines**: Soluble mediators like **IL-1β**, **TNF-α**, and **IL-6** produced by activated immune cells that coordinate inflammatory responses and signal to the brain.
- **Anti-inflammatory cytokines**: Immunoregulatory molecules that down-regulate the **pro-inflammatory cytokine** response.
- **Indoleamine 2,3-dioxygenase (IDO)**: An enzyme that degrades **tryptophan** along the **kynurenine pathway** and is highly inducible by **pro-inflammatory cytokines**.
- **Kynurenine pathway**: The pathway through which the majority of dietary **tryptophan** is degraded, producing several neuroactive compounds.
- **Toll-like receptor (TLR)**: Highly conserved membrane spanning receptor that recognizes pathogenic molecules.
- **Depression-like behaviour**: Behaviour displayed by laboratory animals that mimics some features of clinical **depression**, such as helplessness and anhedonia, and is normally alleviated by antidepressant drugs.