Inflammatory dysregulation

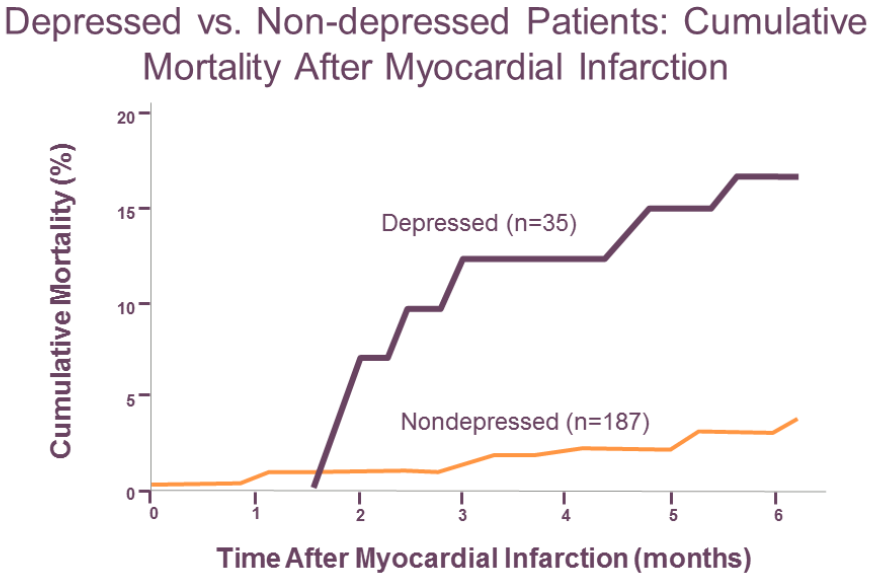
MDD may be more than just a psychiatric disease, as there is evidence of widespread systemic consequences. A literature review of MEDLINE articles published from 1966 to 1997 using the search terms "major depression," "psychiatry," "cardiovascular disease," and "pathophysiology" was used to develop the possible links between MDD and CVD. The literature review includes studies investigating the role of depression in pathophysiological changes related to CVD and studies on the treatment of MDD in patients with CVD.

Neuroendocrine dysregulation and elevated sympathetic tone (activity in the sympathetic nervous system) may result in cardiovascular morbidity and increased risk of metabolic syndrome.

Immune response may be compromised in MDD.

Major depression and depressive symptoms, although commonly encountered in medical populations, are frequently underdiagnosed and undertreated in patients with cardiovascular disease (CVD).

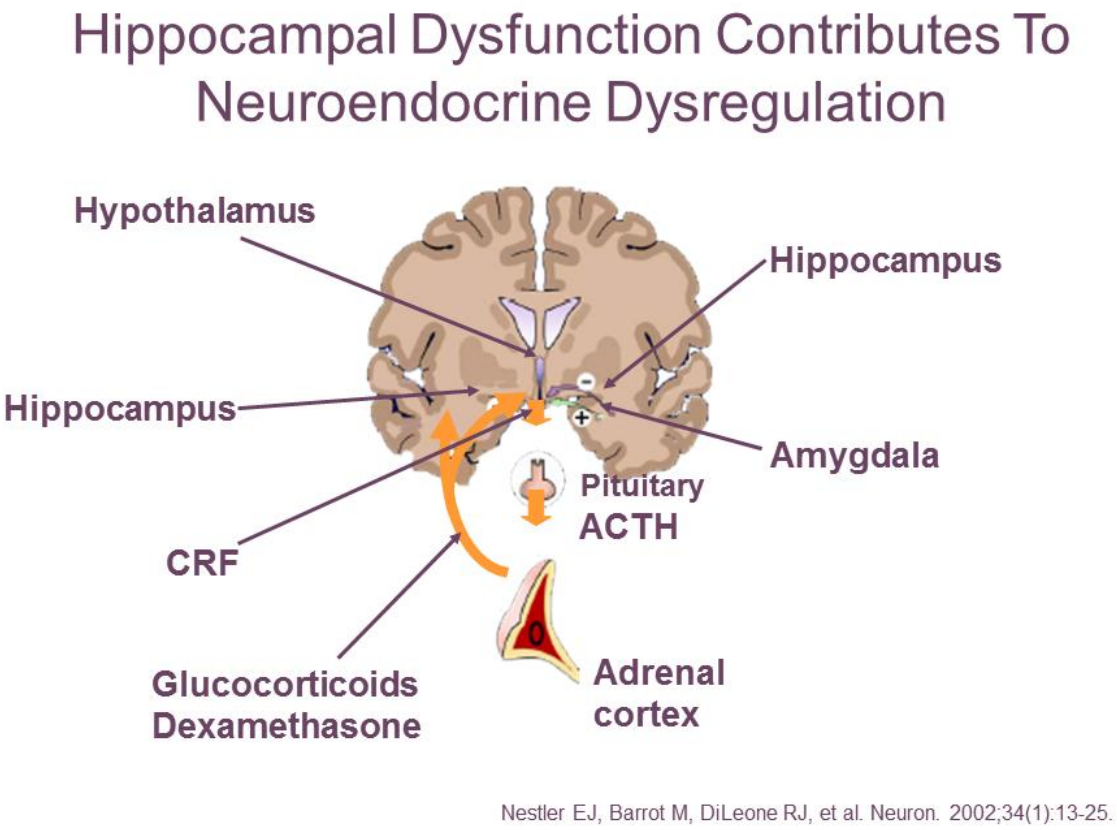
This is of particular importance because several studies have shown depression and its associated symptoms to be a major risk factor for both the development of CVD and death after an index myocardial infarction.



Adapted from Frasure-Smith et al. JAMA. 1993;270:1819.

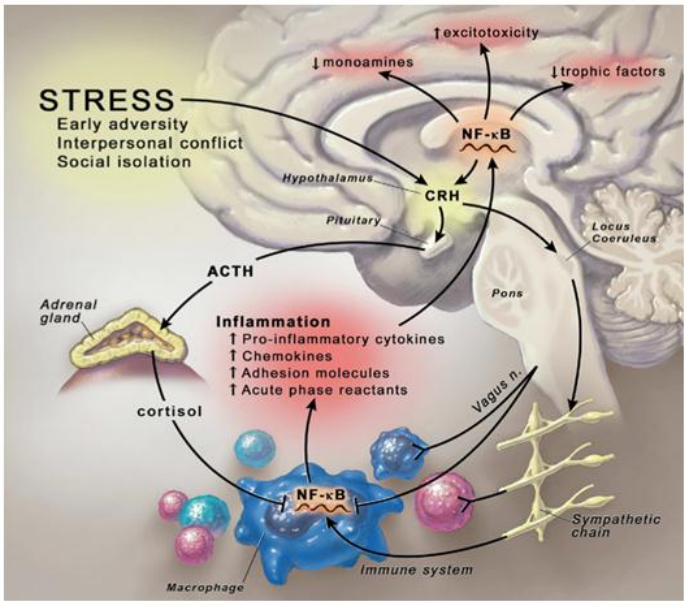
This graph looks specifically at the endpoint of cardiovascular mortality. The data are taken from a well known Canadian study published in JAMA in 1993. It examined mortality in patients post myocardial infarction (MI) among those who had and who did not have depressive symptoms.

As clearly demonstrated in the graph, mortality was significantly and substantially increased in patients with depression following an MI.



During periods of prolonged stress, such as during depressive episodes, normal mechanisms for dealing with stress may malfunction and lead to damage of the hippocampus. This damage can then lead to disruption of feedback loops designed to restore homeostasis, leading to a runaway system and even more neuronal damage.

Neuroendocrine, Autonomic, and Immune Dysregulation in MDD



ACTH=Adrenocorticotropic hormone; CRH=Corticotropin-releasing hormone; MDD=Major depressive disorder; NF-κB=Nuclear factor kappa B.

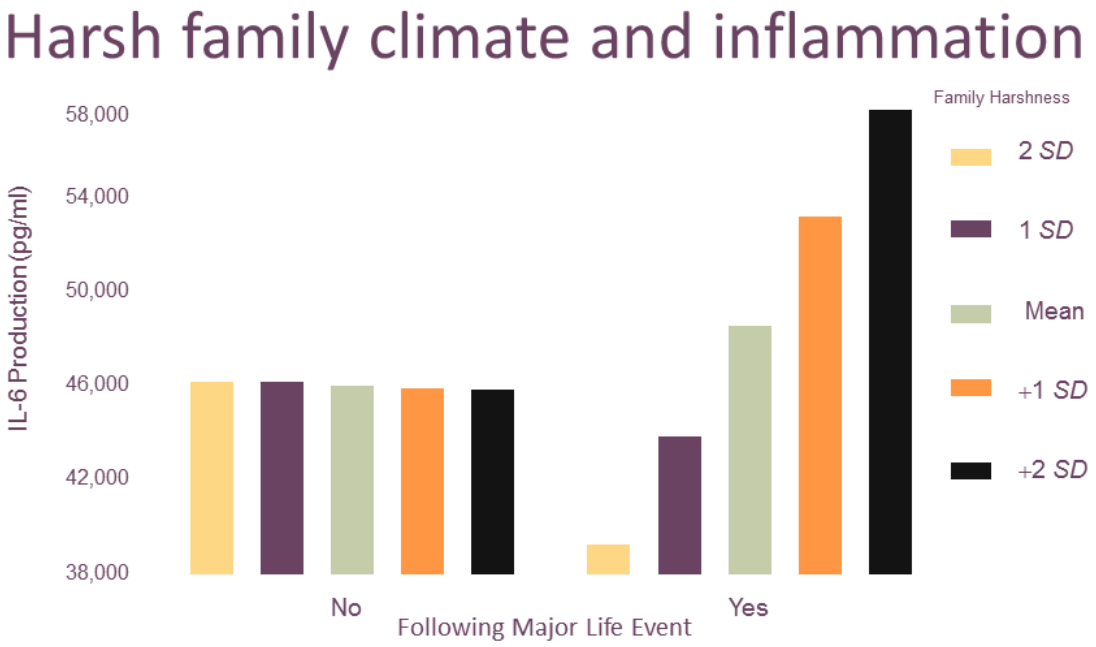
Miller et al. *Biol Psychiatry* 2009;65(9):732-41.

- This picture is a visual representation of how external stressors can provoke an activation of the inflammatory response in the brain.
- The image shows these psychosocial stressors activating the central nervous system stress circuitry, including corticotropin-releasing hormone (CRH) and the sympathetic nervous system pathways via the locus coeruleus.
- Catecholamines can increase nuclear factor-κB (NF-κB) DNA binding in cell types, including macrophages, resulting in the release of inflammatory mediators that promote inflammation.
- Pro-inflammatory cytokines can access the brain, induce inflammatory signaling pathways including NF-κB, and contribute to altered monoamine metabolism, increased excitotoxicity, and decreased production of relevant trophic factors.
- Cytokine-induced activation of CRH and the hypothalamic–pituitary–adrenal (HPA) axis, in turn, leads to the release of cortisol, which along with efferent

parasympathetic nervous system pathways (e.g., the vagus nerve) serve to inhibit NF-κB activation and decrease the inflammatory response.

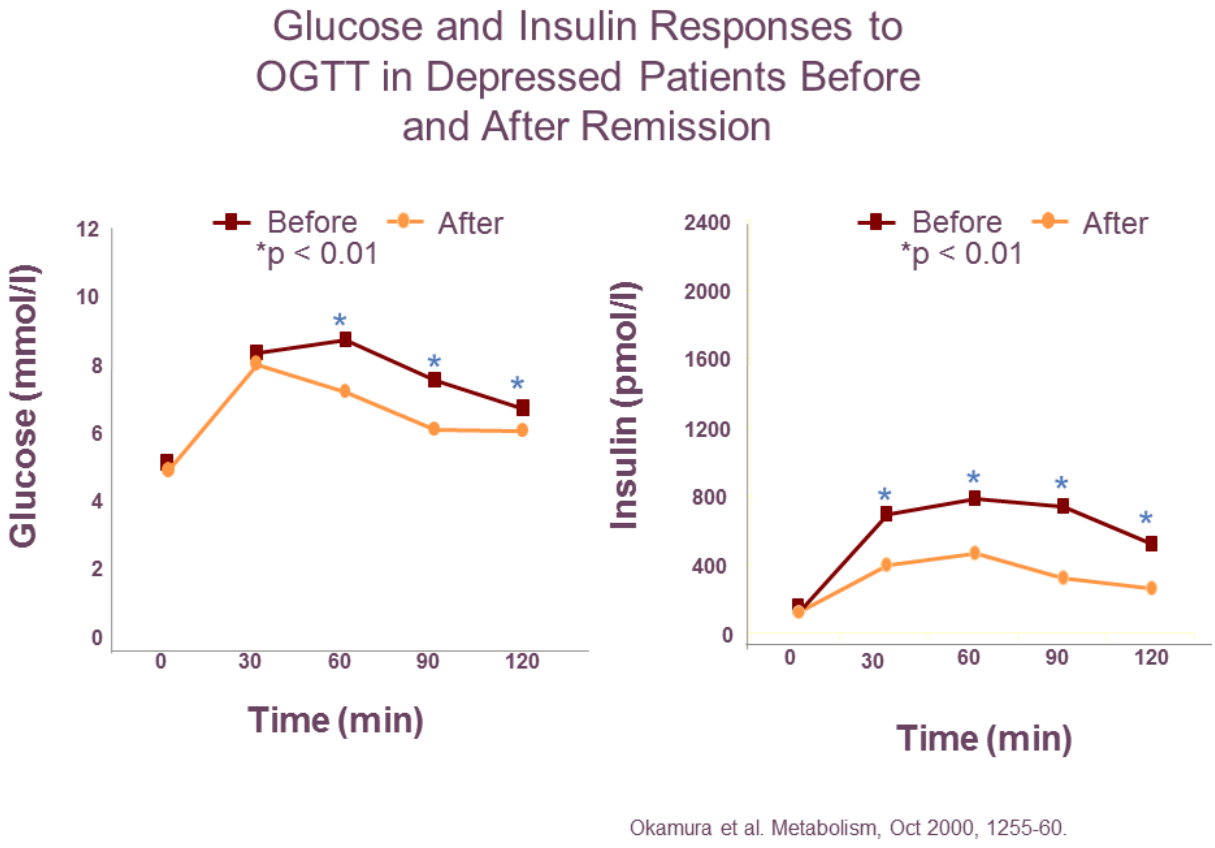
- In the context of chronic stress and the influence of cytokines on glucocorticoid receptor function, activation of inflammatory pathways may become less sensitive to the inhibitory effects of cortisol, and the relative balance between the pro-inflammatory and anti-inflammatory actions of the sympathetic and parasympathetic nervous systems, respectively, may play an increasingly important role in the neural regulation of inflammation.

Inflammation and increased levels of IL-6 interleukin-6 have been found I persons with harsher family environments. Thus nurture and social factors can contribute to physiologic changes and risks for developing systemic inflammation.



Study authors repeatedly measured psychological stress and inflammatory activity in 135 female adolescents on four occasions over 1.5 years. Participants' interleukin-6 (IL-6) production in response to stimulation with lipopolysaccharide. The graph shows levels of IL-6 production following major life events (right side) and levels of IL-6 production not following major life events (left side). The predicted values are shown at five different levels of family harshness.

The figure below demonstrates the association between depression and glucose dis-regulation and diabetes. The association between depression and diabetes has been recognized since the 19th century but still remains poorly understood. What is clear from these graphs is that achieving remission through treatment has an impact on both glucose levels and insulin response to an oral glucose tolerance test.



Okamura et al. Metabolism, Oct 2000, 1255-60.

References:

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Okamura et al. Metabolism, Oct 2000, 1255-60.