

Chapter 13

Depression: Not Just a Top–Down Phenomenon

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Depression can be characterized as a state of mental and physical lethargy in which sufferers report irritability, lack of focus, little or no motivation, lack of interest in previously enjoyed activities, sleep and appetite disturbances, hopelessness, and desired social isolation [1]. It is the second leading of cause of disability worldwide and #1 in the United States of America (USA). In the USA, there is an estimated \$83 billion in economic burden due to depression yearly; 31 % direct medical costs, 7 % suicide-related mortality costs, and 62 % workplace associated costs [2]. While the economic costs to society are staggering, the personal cost of depression to the individual and on one's social network is dramatic.

If untreated, depression can result in substantial impairment in daily functioning. Depression, even at subclinical levels, can lead to substance use and/or abuse, failed or abusive relationships, or loss of employment. Children exposed to depressed parent(s) have an increased likelihood of developing depression [3]; thus, unmanaged depression has cross-generational consequences. Using a multi-disciplinary lens, depression is associated with behavioural, biological, psychological, environmental, and genetic risk factors.

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13.1 Physiological Underpinnings

Depression can occur independently of psychological or physical disease; however, it frequently complicates chronic physical conditions such as cardiovascular disease, diabetes, and cancer [4, 5] and traumatic emotional experiences, suggesting that poor physical health, disrupted physiological functioning, and unresolved emotional experiences and depression may have shared underlying mechanisms.

13.1.1 Neurotransmitter Imbalance

In clinical practice, depression is commonly treated as a neurotransmitter imbalance where patients are prescribed medications to increase the presence of catecholamine neurotransmitters in the brain [6]. For example, monoamine oxidase inhibitors, tricyclic antidepressants, and a variety of reuptake inhibitors including selective serotonin, serotonin-norepinephrine, and dopamine-norepinephrine, are thought to elevate serotonin, dopamine, and norepinephrine in the brain and effectively reduce depressive symptoms.

Medications offer the perception of a quick or easy fix which many patients demand, especially in the USA. However, research pioneered by Dr. Irving Kirsch and colleagues [7] suggest that placebos are just as effective as antidepressants for patients with mild to moderate depression (85–90% of the population) without their negative side effects.¹ In fact, the small benefit provided by antidepressants over the placebo may still have to do with the placebo effect; the negative side effects that patients had may have led to an increased perceived benefit because they knew they were on the drug and not placebo [8]. Due to the ineffectiveness of antidepressants over placebo, and their potential to result in an increase in suicidal/homicidal thought especially early in treatment (FDA-blackbox warning, its strongest available measure short of withdrawing a drug from the market), the neurotransmitter imbalance theory as the cause for depression is largely challenged and at times referred to as a myth [8].

¹What Do These Findings Mean?

These findings suggest that, compared with placebo, the new-generation antidepressants do not produce clinically significant improvements in depression in patients who initially have mild to moderate depression, but show significant effects only in the most severely depressed patients. The findings also show that the effect for these patients seems to be due to decreased responsiveness to placebo, rather than increased responsiveness to medication. Given these results, the researchers conclude that there is little reason to prescribe new-generation antidepressant medications to any but the most severely depressed patients unless alternative treatments have been ineffective. In addition, the finding that extremely depressed patients are less responsive to placebo than less severely depressed patients but have similar responses to antidepressants is a potentially important insight into how patients with depression respond to antidepressants and placebos that should be investigated further (<http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0050045>).

Yet, in the severe and/or treatment-resistant depression, lithium and atypical antipsychotics can augment antidepressant effects of selective serotonin reuptake inhibitors [9]. In addition, repetitive transcranial magnetic stimulation of the right prefrontal cortex and deep brain stimulation² of white matter tracts near subgenual cingulate gyrus or of the subcallosal cingulate gyrus and nucleus accumbens (independently) mitigate depressive symptoms [10–13]. Taken together, neurobiological dysfunction governs severe depression, but these tools only reliably and effectively help a small portion (10–15 %) of those dealing with depression. Thus, for the vast majority of patients with depression, the underlying mechanism(s) of their symptoms may not be brain abnormalities as observed in those with severe depression; time to go beyond the brain.

13.1.2 *Disruption of Homeostatic Hormones*

According to the Diagnostic and Statistical Manual of Mental Disorders 5th edition [1], an individual can be labelled with major depressive disorder if for 2 weeks, they have felt five of the nine following symptoms nearly every day; depressed mood/irritable, decreased interest or pleasure, significant weight/appetite change, disordered sleep, change in activity, fatigue, guilt/worthlessness, decreased concentration, or suicidal thoughts. The major problem with this “definitional symptom” list is that the symptoms can be an exceedingly common occurrence even in healthy people, and they are often caused by a variety of different stimuli related to stress (e.g., diagnosis with a serious medical condition, grief, job loss, relocation, etc.).

The human body consists of a series of complex organ systems that interact and attempt to maintain homeostasis via regulatory hormonal pathways. The neuroendocrine arousal systems are the most widely studied in connection with stress-related diseases, including sympathetic nervous system (SNS) activation leading to norepinephrine and epinephrine release, and stimulation of the hypothalamic–pituitary–adrenal (HPA) axis resulting in the secretion of hormones including corticotropin releasing hormone (CRH), adrenocorticotropin hormone (ACTH), and cortisol [14].

Cortisol mobilizes energy, catalyses protein breakdown, and stimulates the cardiovascular system to ensure oxygen and nutrient supplies to skeletal muscles and the brain. Cortisol naturally peaks 30–45 min post-waking, has an accelerated decline through lunch time, and then slowly declines the remaining time an individual remains awake. This diurnal rhythm varies significantly within a person as

²Andres Lozano: Parkinson’s, depression and the switch that might turn them off. January 2013 at TEDxCaltech
http://www.ted.com/talks/andres_lozano_parkinson_s_depression_and_the_switch_that_might_turn_them_off?language=en.

between people, but does show dyadic synchrony [15]. Due to cortisol's energizing effects, it also is released in response to a stressor. Following the perception of a stressor, the body responds by activating the fight-or-flight SNS and the slower, but longer lasting, HPA axis that remains active until cortisol levels are elevated to provide negative feedback to the brain shutting down the system [16].

Dysregulation of the stress response systems has been associated with depression including, SNS hyperactivity, abnormal diurnal cortisol rhythmicity, and maladaptive cortisol response to stress [14]. For example, depressed individuals have an elevated cortisol response to waking and higher cortisol at bedtime compared to healthy controls [17]. In addition, those who are depressed exhibit an exaggerated hormonal (i.e., CRH and cortisol) response to stress compared to non-depressed controls [17]. This prolonged excessive cortisol production and exposure may be the result of neurons in the hippocampus and hypothalamus reducing their sensitivity to cortisol. However, the type of depression plays a critical role in the underlying biological profile [14, 17].

Melancholic depression,³ or the 'typical' depressive profile, is connected to hyperactivity of stress response systems including elevated norepinephrine, CRH, and cortisol. Atypical depression presents behaviourally and hormonally as the antithesis of melancholic depression; the HPA axis is hypoactive [14] and may contribute to elevated systemic inflammation found in patients with this form of depression [17] (Fig. 13.1).

13.1.3 Excessive Inflammation

Proinflammatory cytokines can produce sickness behaviour or depression-like symptoms including low mood, fatigue, and psycho-motor slowing in otherwise healthy volunteers [18–20]. Thus, the relationship between depression and inflammation has been and continues to be examined thoroughly.

³History: 50 years ago, clinical depression was either endogenous (melancholic) or reactive (neurotic). Endogenous depression was a categorical biological condition with a low lifetime prevalence (1–2%). By contrast, reactive depression was exogenous—induced by stressful events affecting a vulnerable personality. (Parker, G. Is depression overdiagnosed. *BMJ*, 2007;335:328.)
DSM-IV criteria:

- Anhedonia (the inability to find pleasure in positive things) and
- Lack of mood reactivity (i.e., mood does not improve in response to positive events) and at least three of the following:
 - Depression that is subjectively different from grief or loss
 - Severe weight loss or loss of appetite
 - Psycho-motor agitation or retardation
 - Early morning awakening
 - Guilt that is excessive
 - Worse mood in the morning

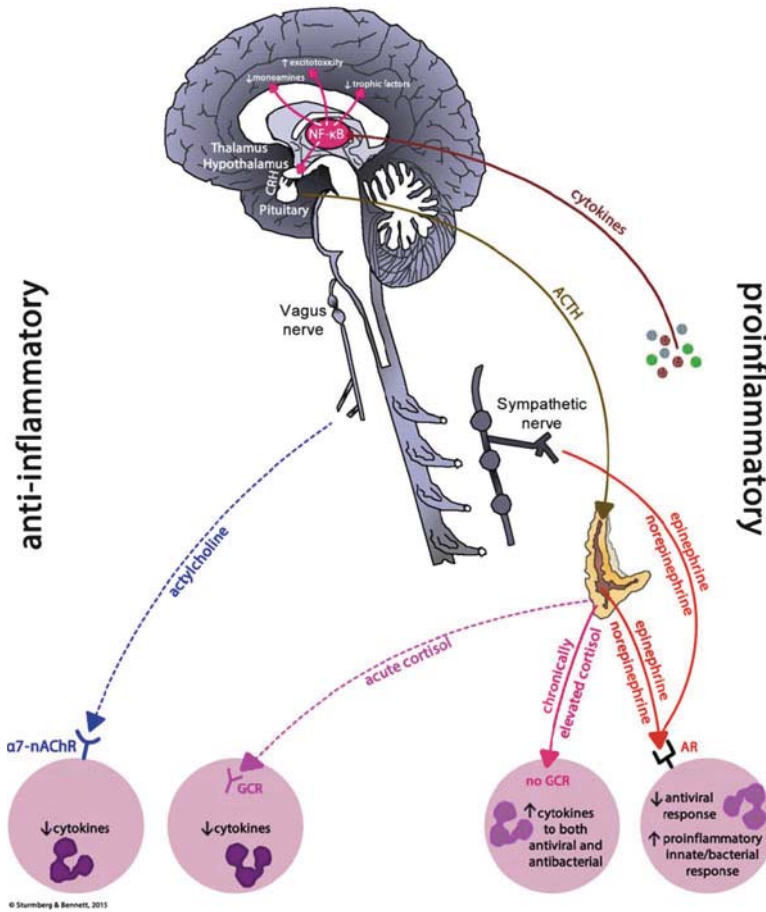


Fig. 13.1 Schematic review of communication between the arousal/stress systems and immune cells during acute and chronic arousal situations. Acute stimulation of the stress systems results in a short-lived innate/antibacterial immune response that diminishes following resolution of the stressor and activation of the parasympathetic nervous system (PNS) during recovery. Chronic stress leads to unregulated cytokine production due to protracted sympathetic activation, down-regulation of the glucocorticoid receptor, and persistent PNS withdrawal. Excessive inflammation stimulates the stress systems and induces sickness behaviour. Dashed lines indicate inhibitory or anti-inflammatory effects and solid lines indicate activating or proinflammatory effects. $\alpha 7$ -nAChR: alpha 7-nicotinic acetylcholinergic receptor, ACTH: adrenocorticotropic hormone, AR: adrenergic receptor, CRH: corticotropin releasing hormone, GCR: glucocorticoid receptor

Both syndromal depression and self-reported depressive symptoms are associated with elevated proinflammatory mediators including IL-1, IL-6, and CRP [21–24]. In addition, as depressive symptoms worsen, inflammatory markers increase; supporting a dose response relationship between depression and systemic inflammation [24, 25]. One mechanism underlying this relationship may be

related to the dysregulated stress reactivity observed in those who are depressed. For example, individuals who are depressed exhibit decreased sensitivity to glucocorticoids' anti-inflammatory effects as well as greater NF- κ B activity compared to those who are non-depressed; resulting in higher IL-6 and TNF- α levels [26, 27]. Thus, excessive NF- κ B activity and decreased responsiveness to glucocorticoids may enhance and sustain production of proinflammatory cytokines in individuals with depression.

The parasympathetic nervous system (PNS) is another potent anti-inflammatory mechanism. Acetylcholine, the neurotransmitter of PNS, can decrease NF- κ B activity via nicotinic acetylcholinergic receptors; resulting in reduced immune cell activity [28]. Thus, the excessive activation of the SNS observed in individuals who are depressed occurs to chronic withdrawal of PNS activity, leading to increased inflammation. Indeed, PNS activity was lower in clinically depressed women compared to healthy controls [29]. Furthermore, the cardiovascular imbalance between the SNS and PNS has been a purported mechanism linking depression to cardiovascular disease [17, 30].

The immune system influences the brain. Cytokines can initiate the HPA axis; they can also modulate the production and metabolism of neurotransmitters such as serotonin, dopamine, and norepinephrine which may play critical roles in depression [31]. In clinical trials, anti-inflammatory medications such as cyclooxygenase-2 inhibitor or aspirin augment the antidepressant effect of serotonin and norepinephrine reuptake inhibitors in clinically depressed individuals compared to those who receive the antidepressant plus placebo [32]. Given that antidepressants are little better than placebo [8], these data suggest that anti-inflammatories may be producing the antidepressant effect—disappointingly these trials did not include anti-inflammatory or placebo arms for comparison.

Recent advances in understanding gut microbiota's role in human behaviour add more ammunition to address chronic disease with a complexity lens. Drs. John Cryan and Timothy Dinan [33] illustrate the connections among gut microbiota, excessive inflammation, and mood; resulting in the emergence of the microbiota-gut-brain axis theory. Although this field is in its infancy, the wide use of antibiotics and antibacterial solutions may also play a significant role in the brain and its behavioural output. Taken together, multi-system dysregulation underlies the heterogeneous experience of depression; suggesting that an understanding of complexity must be applied to successfully help patients with any form of depression.

13.1.4 Co-Morbidity

Chronic physical diseases and depression are often linked—either one is a risk factor for developing the other. Physiological dysregulation of one organ system (e.g., psychological stress, insulin resistance, hypertension, etc.) strains the rest of the body; resulting in adaptations that might not be “healthy” or positive, but allows the

person to survive in this distressed state, as known as allostasis or allostatic load, a theory linking stress to disease popularized by Bruce McEwen, Ph.D. [34].

The acute medical response to a physical or emotional disorder is to treat the immediate system perturbation. For example, if a patient has hypercholesterolaemia, a statin is prescribed to reduce their cholesterol, the primary outcome. However, studies now show that statins have significant anti-inflammatory effects [35]; suggesting that statins may influence a reduction in depressive symptoms that are caused by elevated systemic inflammation. Thus, examining the untoward effects of pharmacological treatment for a chronic physical disease might enable us to understand all the mechanisms actually driving this two-way communication between the brain and the periphery.

13.2 Psychosocial Environment

Individuals do not function in isolation. Health psychologists view an individual through a biopsychosocial lens. To fully understand a person's health, one must consider biological (e.g., genetics, gender, etc.) and physical symptoms, but also psychological and social factors concurrent with physical health and major life events in the present or past. The first physical chronic disease that launched the field of health psychology was cardiovascular disease. Initially, Type A personality, defined as competitive, intense, anxious, and hostile, was linked to an increase incidence of cardiac events—eventually narrowed down to trait hostility [36]. This foreign concept that personality could impact physical health evolved into the examination of individual differences among health outcomes.

Today, when examining the factors that influence depression, health psychologists look at multiple levels including the individual, family, social networks (e.g., work, religious groups, etc.), ethnicity/culture, and even the national and global forces that might be at work. Perceived socioeconomic status (SES) reliably explains health disparities; in a dose-dependent manner, lower SES is associated with greater incidences of depression, cardiovascular disease, diabetes, and dysregulated immune and neuroendocrine function in comparison to higher SES [37–39]. In addition to and often confounded with SES, depression can be explained via individual differences in health behaviours such as tobacco smoking, poor diet, and reduced physical activity, and psychosocial factors like childhood trauma, social isolation, interpersonal stressors, violence, and workplace stress [17]. These factors can impact genomic expression including neurotransmitter production and release, neuroendocrine regulatory pathways, inter- and intracellular metabolism, and the immune system [40, 41]—bringing the depression and chronic disease relationship full circle.

Culturally, those diagnosed with depression are marginalized and often the victim of externalized and internalized stigma [42]. Society and close social networks will explicitly or implicitly tell depressed individuals that they just need to “pull it together” and “stop being so sensitive”. However, stigma and ignorant

understanding of depression increase psychological stress, thus activating the very biological systems underlying the development of depression. Given the strong link between depression and the dysregulated biological systems, we need to use this knowledge to change the general population's perception of mental health and diagnosis. If people understand that what drives depression also advances the development of chronic physical conditions like cardiovascular disease or Type 2 diabetes, then acceptance and early treatment of depression may help avoid the serious escalation that can occur if the brain's perception is left unchecked.

13.3 Predisposed to Depression?

Drs. Raison and Miller [43] suggest that our immune systems have developed a strong inflammatory bias aimed to enhance survival chances in constantly changing, thus challenging, physical environment. This predisposed inflammatory bias, once a positive adaptation, is no longer required in an environment where technological advances have minimized external microbial and existential threat levels. Our inability to counterbalance the proinflammatory bias now appears to be our undoing, as our brains are “unnecessarily” primed to detect and perceive stress and our immune cells efficiently produce inflammatory messengers—releasing a hormonal cascade that taxes multiple organ systems disrupting homeostasis.

Sedentary lifestyles, ample access to calorie-dense foods, and uncontrolled psychological stress amplify our predisposition towards excessive inflammation. For example, inflammation acutely rises to physical exercise; however, individuals who are physically active have lower systemic inflammation than those who are sedentary [16]. Many of the factors that influence inflammation are also independently related to depression [17]. To break the depression–inflammation cycle, there must be a point that interventions and preventative care can target. Luckily, people have control over many of the inflammatory inducing factors including physical inactivity, obesity, anxiety, diet, exercise, tobacco smoking, social support, and sleep. Thus, it is imperative that physicians and the medical/health field as a whole address behaviour because medications cannot solve our complex diseases.

13.4 Imperative for the Twenty-First Century

The transition from a solely symptom focused treatment plan to one that incorporates understanding of the psychosocial components of disease is essential—the most prevalent causes of morbidity and mortality have changed, thus adaptation is necessary. The incorporation of a health psychologist or other health behaviour specialists as an active member in a patient's care team will add the expertise necessary to improve patient outcomes. Similar to physicians, health psychologists and other behavioural health experts may specialize in a specific population such

as psycho-oncology or they may work with a broad population much like a general practitioner educating people on stress management tools. Given the dysregulation of multiple systems, medication alone cannot solve our health problems over the long haul. Primary care must expand to include treatment associated with health behaviour change (i.e., exercise, diet, sleep, etc.) and stress management. Finally, increasing awareness to the imbricate causes of mental and physical health disorders may reduce/diminish stigma and increase pursuit of behavioural health services.

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