REVIEW ARTICLE

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A unifying framework for depression: Bridging the major biological and psychosocial theories through stress

Abstract

Several mechanisms for the development of depression have been proposed, and a comparative examination reveals considerable overlap. This paper begins by summarizing the conclusions drawn in the literature on the major biological theories: HPA-axis hyperactivity, the monoamine theory, the cytokine hypothesis/ macrophage theory, and structural changes to relevant brain regions and neurons. It then discusses the role of psychosocial stress as a bridge between the pathophysiology of depression and its predominantly psychosocial risk factors, touching upon theories offered in psychology and in population health. This paper further proposes a unifying framework which integrates the major theories. The multiple systems involved, and the directional complexity among them, likely help to explain the wide-ranging symptoms associated with depression, and the wide variety of comorbid medical conditions. They may also contribute to challenges in treatment, the diversity in symptoms and treatment outcomes among individuals, and the high rates of symptom persistence and relapse. The apparent bi-directionality of associations may suggest the existence of positive-feedback loops which aggravate symptoms; however, further bench research is required to confirm such phenomena. A better understanding of these interweaving associations is warranted. Additionally, given the significant influence of socioeconomic and psychosocial factors on the aetiology of depression, population-level interventions that address the social determinants of health are required. Current individual-level pharmacologic approaches are designed to treat pathophysiology once it is underway, and current individual-level non-pharmacologic interventions (such as talk therapy) are designed to moderate the relationship between psychosocial stress and pathophysiology. In contrast, a key strategy for primary prevention lies in population-level interventions that address the predominantly social causes of one of depression's most notable risk factors: chronic psychosocial stress.

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Depression is a prevalent psychological disorder. Its symptoms can include persistent depressed mood, lack of interest or pleasure, fatigue, problems in concentration and memory, problems in sleeping, changes in appetite and changes in weight. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) lays out the criteria for clinical diagnosis of a range of depressive disorders (the most severe of which is major depressive disorder), based on the presence, persistence and severity of the above symptoms [1].

Many hypotheses have been suggested regarding mechanisms for the development of depression; these have stemmed from various perspectives within the field of psychology, and range in focus from psychosocial to biological. Even restricting consideration to the literature in the realm of biological psychiatry proposes multiple, seemingly distinct, theories to explain the physiology behind depressive disorders and antidepressant action; however, examination reveals considerable overlap among the various biological theories. This observation suggests that, rather than being competing explanations, the various biological theories on depression may simply be focussing on different components of the overall pathophysiology of depression. A number of thorough review articles are available that offer detailed discussion of the studies supporting each individual biological theory. These articles have been cited throughout this paper. The overlap between physiological mechanisms is discussed in the existing literature, but in a limited manner; areas of overlap with other mechanisms are generally presented as further evidence for the validity of the single theory or mechanism, which is the topic of the given article. A comprehensive integration of all of the major biological theories of depression has not been the focus of other papers.

Bench and clinical research point to biological phenomena as the basis for depressive disorders; however, population health studies point to psychosocial factors, notably socioeconomic status and life stress, as the most significant risk factors for depression [2-4]. The diathesis-stress and biopsychosocial approaches to understanding depression recognize that depression has both biological and social causes; however, much of the literature on the underlying mechanisms of depression continues to be largely fragmented across the broad biological and psychosocial "camps". Mechanistically speaking, is it possible to reconcile the social nature of the population-level risk factors of depression, and the psychosocial focus of psychological theories of depression, with the biological pathophysiology associated with it? As with the question of the overlap between biological theories, the literature does not focus on the mecha-

nistic bridge between social, psychological and biological approaches to understanding depression.

This paper has the following three objectives: 1) to summarize the main conclusions drawn in the literature on each of the major biological theories of depression, 2) to discuss psychosocial stress as a bridge between the social and psychological risk factors of depression and its pathophysiology and 3) to extend this bridge-building further by focusing attention on the mechanistic overlap among the biological theories. The endpoint will be the presentation of a unified framework incorporating the major mechanisms that are believed to contribute to depression. The hypothalamic-pituitary-adrenal axis appears to be a key player, both in the bridge between the broader biological and psychosocial camps in psychology and also between the various theories and mechanisms proposed in the realm of biological psychiatry; accordingly, it will be featured in the proposed framework as the key integrator.

To achieve the above objectives within a single paper, and also to accommodate the diverse and multidisciplinary background of the clinical readership being targeted, mechanistic discussions have been simplified and/or summarized. To make up for this, the authors have pointed to several key review papers throughout this article, for readers seeking more depth on specific mechanisms.

Overview of the major biological theories and mechanisms

The hypothalamic-pituitary-adrenal (HPA-) axis

The hypothalamic-pituitary-adrenal axis is a critical component of the body's key stress response system, and is at the interface between psychosocial stress and the physiological changes associated with it. It involves the hypothalamus (a limbic system brain structure), the anterior pituitary and the adrenal cortex. In response to stress (among other triggers), a chain of events involving corticotrophin releasing hormone (CRH, also known as corticotrophin releasing factor or CRF) and adrenocorticotrophic hormone (ACTH) ultimately yield the secretion of corticosteroids, including glucocorticoids, mineralocorticoids and cortical sex hormones. Two other hormones of relevance are ADH (antidiuretic hormone or vasopressin) and oxytocin, which stimulate and inhibit ACTH release, respectively, thereby impacting HPA-axis activity. The glucocorticoids include the hormone cortisol, which yields a number of physiological consequences aimed at increasing blood glucose levels, suppressing immune function and preparing the body to handle the stressful situation at hand. The HPA-axis is normally regulated by a negative-feedback system: excess cortisol

and excess ACTH will inhibit HPA-axis activity, to keep stress hormone levels (and their effects) in check [5,6].

Continuous elevation of stress hormones, however, impairs this regulatory system, leading to continuous hyperactivity of the HPA-axis [7]. As discussed in a comprehensive 2005 review by Swaab and colleagues, various laboratory studies have implicated CRH [6,8], ADH [6,9], ACTH [6] and cortisol itself [6,10], as causally mediating this hyperactivity. Despite the debate as to the exact physiological mechanisms by which this hyperactivity occurs, there is compelling evidence to suggest, in general terms, that HPA-axis hyperactivity is involved in depression. In patients affected with depression, plasma and salivary cortisol and cortisone levels have been found to be elevated, and the secretion of urinary free cortisol is increased [11]. Individuals with Cushing's Syndrome, which is marked by hypercortisolism due to endogenous secretion of cortisol, often exhibit symptoms of depression [6]. Consistent with the proposed loss of negative feedback, the following have also been observed: decreased corticosteroid receptor function [12], modified responses by the adrenal glands to ACTH and by ACTH to CRH [13], a lack of response to dexamethasone administration [12,14], as well as enlargement of the adrenal [15] and pituitary [16] glands. Furthermore, an increase in plasma levels of androgens in women with depression has been found [17] – an observation that is also consistent with HPA-axis hyperactivity, since the major source of androgens in women is the adrenal gland [6]. This hyperactivity may be due to genetic factors, aversive stimuli early in development, or external life circumstances and stresses [6]. Many of the nutritional risk factors identified for depression may also function through the HPA-axis; deficiencies in nutrients such as zinc, iron, magnesium, selenium, omega-3 polyunsaturated fatty acids, vitamin C, vitamin E, and carbohydrates may contribute to depressive disorders through their impacts on HPA-axis physiology leading to impaired regulation and hyperactivity [18-27]. While the hypothesized risk factors for depression are diverse, psychosocial stress from life events is among the most potent factors that can trigger depressive episodes [2].

Glucocorticoids act on numerous organs and systems in the body, including various regions in the brain, the monoaminergic neurotransmission system, the immune system, the metabolic system and the gonadal/reproductive system. Furthermore, CRH and ADH themselves can also impact various systems in the body [5,6]. CRH is of particular interest in understanding depression. Besides its expression in the hypothalamus, CRH is widely expressed in extrahypothalamic circuits of the central nervous system, where it acts as a neuroregulator to integrate complex humoral and behavioral re-

sponses to stress. The effect of CRH at the pituitary level is augmented by the synergistic action of ADH, which is expressed in the supraoptic and paraventricular nuclei and cosecreted from hypothalamic CRH neurons in response to stress [28]. CRH, in association with ADH, drives the HPA-axis and also responds to alterations in cortisol levels. When HPA-axis negative feedback control is lost in depression, CRH continues to be hypersecreted from hypothalamic and extrahypothalamic neurons. Thus, in addition to elevated levels of cortisol, high levels of CRH have also been reported in the cerebrospinal fluid of depressed subjects (8). Corticoids also increase CRH levels in the amygdala [29]. The amygdala is involved in fear and anxiety reactions, which are heightened in major depressive disorders (MDD); therefore, elevated levels of CRH likely contribute to the overall signs and symptoms in MDD [29, 30-34], as reviewed by Herbert [35]. CRH exerts its action by binding to two types of G-protein-coupled receptors, CRH-R1 and CRH-R2; these share 70% homology in amino acid sequence, with greater divergence in their N-terminal ligand-binding domains, reflecting their different ligand preferences. CRH is a high affinity ligand for CRH-R1 and binds CRH-R2 poorly. CRH-like peptides, Urocortin II and III, bind CRH-R2 with higher affinity than CRH. Urocortin I, on the other hand, binds to both CRH receptors with similar affinities [36-38]. Using *in situ* hybridization and immunological techniques, the expression of CRH and its receptors have been localized in diverse areas of the brain [39,40]. The two receptors are differentially expressed throughout the brain, suggesting that CRH exerts different actions at the central nervous system level via these two receptors. CRH-R1 is expressed in high levels in the neocortical areas, lateral dorsal tegmentum, pedunculopontine tegmental nucleus, hypothalamic nuclei, basolateral and medial nuclei of amygdala, anterior pituitary and cerebellar Purkinje cells. CRH-R2, on the other hand, is localized in more discrete areas, including lateral septum, ventromedial hypothalamus, and cortical nucleus of amygdala. Both receptors are expressed in the hippocampus. By binding to the same receptor, CRH activates different signal transduction pathways in different cells, depending on intracellular context. Clinical studies in humans [41] and studies in animal models [42-44] suggest that stress-induced CRH actions are mediated via binding to CRH-R1.

In summary, impaired regulation of the HPA-axis is considered central to explaining many of the physical, emotional and cognitive symptoms associated with depressive disorders [6]. It may also explain some of the comorbidities often seen with depression; the common involvement of the hypothalamic-pituitary system may account for links between

depression and thyroid disorders, Cushing's Syndrome, esthesioneuroblastoma (vasopressin-secreting tumour), and hypertension [6], as well as cardiovascular disease [45].

The Cytokine Hypothesis / Macrophage Theory of Depression

A number of published review papers have discussed the considerable evidence available to support the involvement of the immune system in depression. Briefly, depression is associated with indicators of inflammatory immune activation, including elevated levels of pro-inflammatory cytokines and elevated levels of positive acute-phase proteins, coupled with reduced levels of negative acute-phase proteins. Furthermore, it is widely noted that many symptoms of depression match with the "sickness behaviour" state that occurs with immune activation (e.g., in cases of infection or with cytokine administration) [46-51].

More specifically, macrophages in the periphery and in the brain appear to be activated in depression to secrete increased amounts of pro-inflammatory cytokines such as tumour necrosis factor (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6). These cytokines, in turn, activate cyclooxygenase and nitric oxide synthase activity, yielding inflammatory outcomes. Pro-inflammatory cytokines have been shown to induce many of the physiological and psychiatric symptoms of clinical depression, including changes in eating behaviour, sleeping behaviour, mood, memory, concentration and lack of pleasure. Studies have found that cytokine levels in depressed patients are often higher than normal [46-51], and pharmacologic administration of cytokines (for treatment for diseases such as hepatitis C and some cancers) can also induce symptoms of depression [46, 47, 49, 50]. Furthermore, antidepressants have also been shown to normalize elevated cytokine levels [46, 47, 49, 50]. Cytokines, thus, have been heavily implicated to be causally associated with depression [46-51]. Studies have shown that the inflammatory prostaglandins that stem from these cytokines also appear to suppress many components of cellular immunity (e.g. natural killer cells, T-lymphocytes, neutrophils) and to increase non-specific immune elements such as the complement factors. This is consistent with observations in many studies of depressed individuals [47]. Inflammatory and other immune-related disorders such as (but not limited to) allergies, asthma, cardiovascular disease, multiple sclerosis and rheumatoid arthritis are common comorbidities with depressive disorders [46,52]. Many of the nutritional risk factors for depression appear to impact immune function and inflammatory pathways, and thus likely contribute to depressive disorders through immune mechanisms; these include deficiencies in nutrients

including omega-3 polyunsaturated fatty acids, selenium, iron, vitamin C and vitamin E [18,21,24,26,27,53].

It should be noted that not all studies have reached consistent conclusions on the precise relationship between the immune system and depression. Notably, there is debate surrounding the degree and exact nature of cell-mediated immune activation observed [52]; however, there is compelling evidence that the immune system is involved and that its involvement is primarily mediated through pro-inflammatory cytokines [46,50,52].

The Monoamine Theory of Depression

Communication in the central nervous system is by way of neurons (nerve cells), which receive signals from sensory receptors or from other neurons in the body and transfer this information along the length of the axon. Impulses, known as action potentials, travel the length of the axon of the neuron and invade the nerve terminal, thereby causing the release of neurotransmitter into the synapse (the gap between the axon terminals of one neuron and the dendrites of the next neuron). Neurotransmitters are chemical messengers; in chemical synapses, neurotransmitters are enclosed in thousands of membrane-bound vesicles at the nerve terminal. When the action potential reaches the nerve terminal and depolarization occurs, neurotransmitters are released into the synapse, from where they move to act on receptor proteins embedded in the target neuron's membrane. Depending on the nature of the receptor, the effect of neurotransmitter on the target cell may be excitatory or inhibitory. The neurotransmitter is removed from the synapse in a variety of ways, including reuptake for reuse or degradation, degradation at the synapse, or diffusion away from the synapse. The concentration of neurotransmitter at the synapse is controlled by regulatory receptors. "Autoreceptors" are regulatory receptors that are present on the same neuron releasing the neurotransmitter, whereas as "heteroreceptors" are present on another neuron, releasing a different type of neurotransmitter [54].

Broadly speaking, the monoamine theory of depression suggests that a decrease or deficiency in brain monoaminergic activity results in depression. The monoamines are a group of central nervous system neurotransmitters that include dopamine, norepinephrine (also known as noradrenaline) and 5-hydroxytryptamine (5-HT, also known as serotonin). Norepinephrine and dopamine are further classified as catecholamines; they share a common pathway in their synthesis as they are synthesized from the same precursor (tyrosine). In contrast, serotonin is synthesized from tryptophan. Synthesized in the presynaptic nerve terminal, monoamines are brought into stor-

age vesicles by way of vesicular monoamine transporter [55], and then released by exocytosis into the synaptic cleft through a Ca^{2+} -dependent process [56,57]. Monoamines act on post-synaptic or presynaptic receptors, which are coupled to ion channels or G-proteins [58]. The termination of the actions of all monoamines is via active reuptake into the presynaptic neuron and/or glial cells; reuptake mechanisms involve Na^+/Cl^- dependent transporters, and the processes are dependent upon the membrane potential [59,60]. The intra-neuronal metabolism of the monoamines involves enzymes such as monoamine oxidase (MAO; MAO-A metabolizes serotonin and norepinephrine, MAO-B metabolizes dopamine) and catechol-O-methyltransferase (COMT) [61,62].

Of the monoamines, serotonin and norepinephrine have been implicated in unipolar depressive disorders. While there does not appear to be a strong role for dopamine in the development of unipolar depressive disorders, it is of interest in studying antidepressant drug effects [61]. Serotonergic neurons are found in nine types of nuclei lying in or adjacent to the midline (raphe) regions of the pons and upper brainstem. The dorsal raphe nucleus (DRN) is the largest of the brainstem serotonergic nuclei, and makes major contribution to the enervation of the cortical regions and the neostriatum. The median raphe nucleus (MRN) forms the largest cluster of 5-HT neurons in the mammalian central nervous system, and makes a major contribution to the enervation of the limbic system [61]. There are at least 14 distinct serotonergic receptor subtypes, grouped into three subgroups. Of these subtypes, the most significant is 5-HT_{1A}. This G-protein-coupled receptor is found in large numbers on the serotonergic cell bodies and dendrites of the DRN and on the nerve terminal of the forebrain projection areas of the frontal cortex, the hippocampus and the amygdala. 5-HT_{1A} is inhibitory in function, and thus inhibits the release of 5-HT. The noradrenergic system is found in most brain regions. In the context of understanding depression, its presence is notable in the thalamus, dorsal hypothalamus, hippocampus and cortex [63]. There are three families of adrenergic receptors, all of which are coupled to G-proteins: α_1 , α_2 , and β . The α_1 receptors are generally excitatory in nature. In contrast, α_2 receptors are generally inhibitory in nature; they have been implicated in the inhibitory control of adrenergic and serotonergic pathways innervating the frontal cortex [64].

The monoamine theory of depression was initially based on observation of the effects of antidepressant drugs. The “old” monoamine theory revolved around the basic idea that a decrease or deficiency in brain monoaminergic activity results in depression. According to this idea, antidepressant drugs are believed to increase monoaminergic activity, either by inhibit-

ing the reuptake of neurotransmitters (thereby increasing their availability at the synapse), or by inhibiting their metabolism by MAO (thus increasing the amount of monoamines stored and released) [65]. Further research, however, has permitted evolution of this theory. The “modern” monoamine theory of depression states that an acute increase in monoamine levels at the synapse is likely only an early part of a complex path leading ultimately to antidepressant effects [66]. This acute increase is believed to cause desensitization of the inhibitory auto- and hetero-receptors in certain brain regions, resulting in higher central monoaminergic activity and subsequent mood elevation. Therefore, the antidepressant effect is assumed to stem from the long-term adaptive changes in the monoamine auto- and hetero-regulatory receptors, rather than simply from changes in the levels of the monoamine neurotransmitters. As discussed in the thorough 2004 review by Elhwuegi, various studies on adrenergic receptors have concluded that central α_2 autoreceptors (which inhibit the release of norepinephrine) and α_2 heteroreceptors (which inhibit release of serotonin from the serotonergic nerve terminal) are hypersensitive in depression. This hypersensitivity results in low aminergic activity in the prefrontal areas of the brain. A desensitization of these receptors (via antidepressant drug activity) would yield an increase in both serotonin and norepinephrine at the synapse. Antidepressants may also work by increasing the sensitivity of stimulatory α_1 receptors [61]. There is also evidence from various studies that β adrenergic receptors may be downregulated following antidepressant treatment, though this does not likely contribute to antidepressant action [61]. Studies on serotonergic receptors have concluded that antidepressant therapy action may be through the desensitization of the somatodendritic 5-HT_{1A} and the terminal 5-HT_{1B} autoreceptors (both of which are inhibitory), yielding an increased efficacy of the serotonergic system. Furthermore, the desensitization of 5-HT_{1A} receptors located in the dorsal raphe nucleus, limbic and cortical regions of the brain are observed in antidepressant therapy. Antidepressant-mediated desensitization of 5-HT_{1A} receptors located in the hypothalamus is also observed [61,67,68].

The monoamine theory of depression may help to account for certain comorbidities seen with depression; for example, common pathophysiology involving the serotonergic system may explain the link with migraine headaches [69] and cardiovascular disease [70-72]. Furthermore, many of the nutritional risk factors for depression appear to involve monoamines; deficiencies in nutrients such as folate, vitamin B12, zinc, iron, vitamin B6, omega-3 polyunsaturated fatty acids, vitamin C and carbohydrates may contribute to depressive disorders through

their impacts on the physiology of monoamine neurotransmission [18,19,23,73-78].

While the “modern” monoamine theory addresses a number of the criticisms levelled at the original monoamine theory, points of ambiguity remain. As discussed in detail by Elhwuegi, studies done on the role of adrenergic and serotonergic receptors in depression and antidepressant action have not all reached consistent conclusions. Despite the debate on the exact mechanisms of action, the evidence is still compelling that the adrenergic and serotonergic systems are involved in depressive disorders [61].

Brain structural integrity

Depression has been associated with structural damage or abnormalities in certain brain regions and neurons. Broadly speaking, the brain can be compartmentalized into regions for the purpose of study, based on either structural or functional divisions. When making divisions by function, a region of interest in the context of mood disorders is the limbic system [62,79]. The limbic system is a group of brain structures that promote survival via their influence on emotion, motivation and memory. It includes the hypothalamus, the amygdala and the hippocampus [62,79]. Limbic system structures, in general, are innervated by both noradrenergic and serotonergic projections [61,62].

While all three limbic structures have been strongly implicated in depressive symptoms, the hippocampus has proven to be of particular interest in recent studies. A decrease in hippocampal volume has been associated with both stress [80] and major depressive disorder [81]. The hippocampus also has the highest density of receptors for corticosteroids within the brain and has been linked to the brain's response to stress and to HPA-axis activity regulation [82-85]. Furthermore, the monoaminergic and glutamatergic systems in the hippocampus are implicated in depressive disorders (detailed review on this topic by Joca and colleagues [84]). The role of the hippocampus in stress and depression has been the subject of a number of detailed review articles (e.g., by Dranovsky and Hen [83], Joca and colleagues [84], McEwen [80] and Videbech and Ravnkilde [81]).

Since the different regions in the brain are interdependent, brain regions outside of the limbic system are also believed to be involved in depression. The prefrontal cortex (a structure involved in working memory) is, in particular, implicated. Various studies show morphological changes (cell loss) in the prefrontal cortex in major depressive disorder (e.g., by Banasr and colleagues [86]; review by Swaab and colleagues [6]).

The alteration of hippocampal and other brain region structures through neuronal atrophy and cell loss, associated with prolonged stress or glucocorticoid action, has stimulated intense research interest in the role of neurotrophic/growth factors in neurogenesis, especially those responsive to corticoids. A variety of neurotrophic/growth factors are implicated in the survival and function of neurons in the central nervous system (reviewed by Duman and Monteggia [87]). Aside from members of the nerve growth factor (NGF) family (neurotrophins) - namely, NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) - this ever-growing list includes fibroblast growth factor 2 (FGF-2), insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF). These neurotrophic/growth factors exert their action by binding with high affinities to specific members of the family of tyrosine kinase receptors: TrkA (tropomyosin-related kinase A) (NGF), TrkB (BDNF, NT-4), TrkC (NT3), IGF-1R (IGF-1), VEGF-R (VEGF). Neurotrophins also bind to a low-affinity receptor, termed the p75 neurotrophin receptor (p75NTR) (reviews by Chao [88], Duman and Monteggia [87]). Although it binds biologically-active mature (processed) neurotrophins with low affinity, the p75NTR also binds precursor pro-neurotrophins with high affinity and induces apoptosis by interacting with sortilin [89,90]. Neurotrophins are involved in the regulation of neural development, survival, function, and plasticity [91]. NGF and other members of the neurotrophin family have been shown to induce neurite outgrowth in culture, providing important evidence for the role of neurotrophins in axonal guidance and neural connectivity [92-94]. In the developing brain, neurotrophins are envisaged to play a crucial role in establishing intricate neural networks that persist throughout life. Among the neurotrophins, BDNF, which is highly conserved in vertebrate evolution, has been studied extensively and has been shown to play an important role during brain development and in synaptic plasticity (as reviewed by Cohen-Cory and colleagues [95]). Deficits in BDNF function are implicated in a number of neurodevelopmental, neurodegenerative and neuropsychiatric disorders that are associated with abnormalities in synaptic plasticity [96-99]. MDD is characterized by neuronal atrophy and cell loss in key limbic regions of the brain, especially affecting neuronal plasticity in the hippocampus. The disordered plasticity in MDD is reversed, and normal function restored, by the action of antidepressants. The hippocampus expresses high levels of glucocorticoid receptors and mineralocorticoid receptors [80,100-104]. The hippocampus also expresses high levels of BDNF and its principal receptor, TrkB [35,105]. A number of studies involving animal (rodent) models of stress and/or

depression have shown that exposure to acute or repeated stressors decreases adult neurogenesis in the hippocampus, with a concomitant decrease in hippocampal expression of BDNF (reviews by Duman [103], Duman and Monteggia [87]). Also, administration of corticosterone reduces the mRNA expressions of BDNF and TrkB receptor in rat hippocampus [106,107]. Consistent with observations in animal models, BDNF levels have also been shown to be reduced in the hippocampi of suicide victims in postmortem studies [108-110]. Similarly, the BDNF signaling cascade, the extracellular regulated kinase pathway, has been found to be decreased in suicide victims [109].

The issue of neuronal structural integrity is also causally relevant in depression. As a major oxygen consumer, the brain is quite vulnerable to oxidative stress. Neuronal membranes are very susceptible to lipid peroxidation due to their high polyunsaturated fatty acid content. Peroxidation of nerve endings impacts neurotransmitter transport and therefore affects central nervous system functioning [112]. Hyperhomocysteinemia has been implicated in a wide range of physical and mental medical disorders, including depression. The resulting inhibition of methyltransferase reactions can impact the structure and function of DNA, proteins, phospholipids, cell membranes, receptors and catecholamine neurotransmitters. A number of mechanisms have been proposed for its neurotoxicity, including excitotoxicity and free-radical stress. In neuronal cell culture studies, it has been observed that homocysteine tends to react with transition metals such as copper, resulting in oxidative toxicity and neuronal cell damage – again, impacting neurotransmission and central nervous system functioning [113,114]. A number of nutritional risk factors for depression may contribute to depression due to their impacts on neuronal structural integrity. Deficiencies in folate, vitamin B12 and vitamin B6 lead to hyperhomocysteinemia, which can lead to neuronal damage [113]. Vitamin C, vitamin E and selenium are antioxidants and deficiencies may lead to neuronal damage via oxidative stress [115,116]. Iron deficiency alters myelination [19,76]. Finally, polyunsaturated fatty acids are a key component of neuronal membranes, and thus deficiencies may impair structure and function [18,23,24].

Brain structural integrity may help to explain the link between depression and certain comorbid health conditions; for example, the link between depression and stroke may be due to the occurrence of lesions in brain regions such as the prefrontal cortex or the hippocampus [6,117]. Similarly, the link between depression and type 2 diabetes may also be accounted for through the common occurrence of atrophy in the hippocampus [117]. The link between depression and cardiovascular

disease may be due to hyperhomocysteinemia [18]. Head injuries are also linked to increased likelihood of depression, also likely due to sustained damage to relevant brain regions [6].

Psychosocial stress – bridging social, psychological and biological factors in depression aetiology

Increased HPA-axis activity appears to be correlated with almost all environmental and genetic risk factors for depression, with a return to normal activity levels with treatment or remission [6,118]. While the hypothesized risk factors for depression are diverse, psychosocial stress from life events is among the most potent triggers of depressive episodes. As detailed earlier in this paper, the HPA-axis is activated in response to stress. Intense or chronic stress results in continuous elevation of stress hormones – a condition that eventually impairs the negative-feedback mechanisms normally in place to regulate HPA-axis activity, leading to continuous hyperactivity.

Animal models of depression are largely based on the impact of stressful situations on both the behaviour and the physiology of laboratory animals, notably mice and rats. In the chronic mild stress model, animals are exposed to stressful situations in a chronic but unpredictable manner. In the social defeat stress model, the animals being tested are deliberately placed with more aggressive animals, yielding stressful social interactions. In the learned helplessness model, animals are subjected to uncontrollable and unpredictable stressors while restrained. In the latter model, it is found that even when the restraint is removed, the animals do not seek to escape the traumatic situation. In all three of the models, depression-like symptoms are exhibited by the animals, such as anhedonia, diminished sexual behaviour, decreased investigative and cognitive capacity, weight loss and deteriorated physical (coat) state. Physiological measures also show neurobiological and neuroendocrine changes consistent with chronic stress and depression, including elevation of glucocorticoids from HPA-axis hyperactivity [119]. In the learned helplessness model, the animals exhibit helplessness categorized by deficits in behavioural coping, associative learning and emotional expression [119,120]. In extending this observation to human depression, the learned helplessness model has been used to explain why depressed individuals often feel trapped and unable to escape the negative circumstances in their lives [120].

It should be noted that there is considerable individual variability in the degree of HPA-axis activation to stress. This may be due to inherent physiological differences between individuals, as well as differences in type and perception of stress. An individual's initial HPA-axis activity set-point is genotypically programmed; however, it can be altered by prenatal influ-

ences (i.e., exposures while *in utero*) and by negative early-life events [121]. Prenatal chemical stressors (e.g., mother smoking) may sensitize an individual for later development of depression, notably in children with either a heavy or light birthweight [122]. Low birthweight is also a risk factor in an altered HPA-axis set-point and development of depression later in adulthood [123]. Maternal prenatal stress, maternal stress during child's infancy and maternal stress during childhood all sensitize a child's HPA-axis response to later exposure to stress. Similarly, stressful life events early in childhood (e.g., bereavement or child abuse) also appear to predispose to depression and/or anxiety disorders later in life, likely via programmed, permanent hyperactivity of the HPA-axis [6,82].

During pregnancy, placental 11 β -HSD2 enzyme acts as a protective barrier for the fetus by inactivating high maternal glucocorticoid. Severe maternal stress during pregnancy can saturate the placental 11 β -HSD2 enzyme, exposing the fetus to increased cortisol levels and affecting the HPA-axis of the offspring postnatally. In human pregnancy, severe maternal stress is associated with neuropsychiatric disorders in offspring, implying prenatal programming. The molecular mechanisms envisaged in such prenatal programming involve epigenetic changes, such as DNA methylation, which affect expression of specific genes, including glucocorticoid receptor gene [124]. Research findings on epigenetic mechanisms and DNA methylation in this regard, however, have not been conclusive [125].

In regards to early childhood experiences yielding a predisposition to depression, an integrative link can be drawn with the psychoanalytic perspective of psychology, which emphasizes the importance of adverse experiences in early childhood in the later development of depression [126]. Attachment theory, developed initially by John Bowlby and expanded by various other scholars, is an example of a well-known theory stemming from the psychoanalytic perspective of psychology. In developmental psychology, attachment theory has been applied to explain how traumatic events that disrupt healthy early-life attachments with parents or caregivers, such as parental loss or child abuse and neglect, can contribute to life-long psychopathologies such as depression and anxiety [127]. A 2003 literature review by Beatson and Taryan summarizes evidence showing that adverse early-life relational experiences can yield activation of the HPA axis, leading to sensitization of pathways in the brain related to depression. They conclude that secure attachment acts as a buffer against depression, whereas insecure attachment predisposes individuals to depression and other psychiatric disorders triggered by psychosocial stress [128].

Differential activation of the HPA-axis based on type and perception of the specific stressful situation at hand has also

been observed in various studies [129]. The idea that the specific nature of stressful events and the subjective perception of stressful situations are important to the development of depression, is also central to a number of the non-biological theories of depression that stem from the various perspectives in psychology. The reinforcement theory of depression, stemming from the behaviourist perspective of psychology, suggests that depressed individuals are unable to gain social reinforcement from others due to a lack of necessary social skills [130]; this theory may be thought of both in terms of the fact that dysfunctional social interactions are a source of stress and that social support is a crucial buffer against the negative impacts of stress. In the realm of the cognitive-behaviourist perspective, the well-recognized attributional theory of depression suggests that individuals who are depressed attribute negative occurrences in their lives to factors that are internal (i.e., personal characteristics), stable (i.e., unlikely to change) and global (i.e., broad life impact) [131]. In the cognitive perspective, Aaron Beck's seminal cognitive theory of depression postulates that depressed individuals overgeneralize from stressful life events and maintain a negative view of themselves, their present life and their future (i.e., the "cognitive triad") [132]. While numerous theories have subsequently stemmed from the cognitive perspective in psychology, most are related to Beck's original theory [133]. Another well-recognized concept emerging from the cognitive perspective is that of rumination, which suggests that individuals who think more about the negative, stressful components of their lives are more likely to fall into depression [134]. The link between maladaptive patterns of thoughts (i.e., negative cognitive schemas) and life stress has been conceptualized in terms of cognitive reactivity to stress and cognitive vulnerability to depression in the face of stress, and are reviewed in detail elsewhere [133,135]. The humanistic perspective in psychology argues that psychological disorders such as depression stem from stress associated with the process of self-actualization; an incongruence between one's actual self and one's public self, stemming from trying to live up to the demands of others, leads to distress and depression [136]. While the various theories across the perspectives in psychology differ in terms of the pathways proposed, most involve or implicate experiences of stress. In this regard, it can be summarized that a positive outlook on one's self and one's life, as well as a strong network of social support (intimate partner, family, friends and community) are effective at buffering the emotional and biological impact of stressful life situations – whereas a lack of this support serves to aggravate the vulnerability of falling into depression because of a more negative perception of stressful circumstances and a corresponding inability to cope [137]. Im-

paired coping ability, helplessness and hopelessness in the face of stressful situations all have been shown to contribute to HPA-axis activation [138].

Polymorphisms of certain genes related to the physiological systems implicated in depression appear to make individuals more susceptible to depression when they are faced with adversely stressful events. One such gene is the serotonin transporter gene (5-HTT). By regulating 5-HT transport into (reuptake) and release from presynaptic neurons, serotonin transporters determine the duration and amount of synaptic 5-HT available for post-synaptic response. In so doing, serotonin transporters play an essential role in the fine-tuning of serotonergic neurotransmission. A functional polymorphism of the 5-HTT gene has been identified [139]. The polymorphism (5-HTTLPR) involves a length variation in a repetitive sequence in the promoter region of the gene, in which the s allele is 44 nucleotides shorter than the l (long) allele. The polymorphism results in reduced transcription of the s allele compared with the l allele. In rhesus monkeys, the analogous 5-HTTLPR s allele is associated with decreased serotonergic function (lower 5-hydroxyindoleacetic acid concentrations in cerebrospinal fluid). In a compelling study, Caspi and colleagues [140] have demonstrated that the s allele conferred risk for MDD only in persons who have experienced multiple adverse life events. The study, which has been subsequently replicated with another cohort [141], provides evidence for gene-environment interaction in the aetiology of depression [140]. The human BDNF gene is also a pertinent example. BDNF (rs 6265: Val66Met) is a common variant of the human BDNF gene. At least one copy of the Met allele of the gene is carried by about 30% of humans [35]. The Met allele is associated with a decrease in activity-dependent secretion of BDNF and reduced processing of precursor pro-BDNF to mature BDNF. Carriers of Met allele have been reported [142] to have smaller hippocampi and poorer episodic memory. ProBDNF binds to p75NTR receptor only. Recall that by binding neurotrophin ligand, p75NTR may promote apoptosis through interaction with sortilin (as discussed earlier). Studies to relate BDNF Val66Met polymorphism to predict the risk for MDD have been inconsistent [35]. A study by Bukh and colleagues [143] found the Met allele of BDNF to be associated with MDD following exposure to adverse life events; however, a subsequent study of meta-analysis found only modest association with MDD in males only [144]. A final example is the human FKBP5 gene: FKBP5 is a protein that binds glucocorticoid receptor chaperone hsp90 (heat-shock protein 90) and acts as a co-chaperone to modulate glucocorticoid receptor function. FKBP5 acts as an inhibitor of glucocorticoid-receptor-mediated glucocorticoid action. Sev-

eral single nucleotide polymorphisms (SNPs) have been identified in the FKBP5 gene [145,146], some of which are associated with an incomplete normalization of stress-elicited cortisol secretion in healthy subjects after psychological stress [147]. Zimmermann and colleagues [148] have reported that subjects homozygous for the investigated minor FKBP5 alleles (five SNPs: rs 3800373, rs 1360780, rs 4713916, rs 9296158, rs 9470080) are particularly sensitive to the effects of severe psychological trauma. In a ten-year prospective study, the authors concluded that exposure to severe trauma during childhood and adolescence is a strong risk factor for developing subsequent depression in genetically susceptible individuals [148]. Taken together, the operation of these gene polymorphisms point to a key role for psychosocial stress, cortisol and the HPA-axis in the gene-environment interactions that are believed to contribute to depression.

Socioeconomic and sociocultural factors can strongly influence both the absolute level of, and the perception of helplessness in the face of, psychosocial stress, and this fact ties in with the social-cultural perspective in psychology, which argues the influence of social and cultural factors in the symptoms and prevalence of psychological disorders such as depression [149]. In population health research, there is increasing emphasis being placed on the social determinants of health, as detailed in a recent report by the World Health Organization [150]. These determinants include factors such as income, employment, education, social and physical environments and social support – all of which have been found to be associated with depression [3,4]. While the pathways linking these social determinants with health outcomes are likely complex, it is arguable that the chronic life stress generated from social disadvantage can serve as a perpetual activator of the HPA-axis, leading to deregulation and pathophysiology.

Areas of convergence of the major mechanistic theories

At first glance, the above distinct theories and mechanisms may seem like competing explanations for the pathophysiology of depressive disorders; however, there is considerable overlap between them. There is considerable evidence of multi-way interactions between pro-inflammatory immune function, brain and neuron structures, brain adrenergic and serotonergic systems, and the HPA-axis. Accordingly, a unifying framework that integrates the major theories is being proposed in this paper, and is depicted pictorially in Figure 1. The individual pathways in the diagram are discussed below. In the proposed framework, hyperactivity of the HPA-axis appears to be a key integrative component, both in its link with psychosocial stress, and its links with the other three major physiological

Note: The paths labelled A to G are each discussed under separate headings in the text of the paper

FIGURE 1. A proposed framework to integrate the major physiological mechanisms of depressive disorders, with each other and with social and psychological determinants.

systems involved in the development of depression. The areas of interaction among the major theories are outlined below.

The impact of psychosocial stress on the HPA-axis

The link between chronic life stress and HPA-axis deregulation has been discussed above. In psychology, an increasing emphasis is presently being placed on a biopsychosocial or diathesis-stress-based approach to understanding depression and other affective disorders. This approach states that depression stems from the interaction between biopsychological vulnerabilities (stemming from biological, cognitive, emotive, environmental and social factors, which either predispose or protect against

distress) and stressors, such as stressful life events [151,152]. Mechanistically, HPA-axis stress physiology is important to understanding the biopsychosocial interface in this regard. Figure 1 depicts various social determinants that can lead to psychosocial stress, as well as various types of vulnerabilities (categorized as biological, psychological and social) that can aggravate the pathophysiological impact of psychosocial stress.

An example that illustrates the importance of taking an integrative, biopsychosocial view of depression, is the question of the much higher prevalence of depression in women compared to men. In discussing the health of men and women, both sex and gender are relevant: sex entails the biological differences between males and females, whereas gender encom-

passes the social implications of being a man or a woman [153]. The striking difference in prevalence may in part be attributable to gender-based differences in the expression and the experience of depressive symptoms, bias in diagnosis, and likelihood to seek out help; all these factors have ramifications vis-à-vis the identification of depression [154]. Even if these sources of bias lead to an exaggeration of the true magnitude of the difference, there are mechanistic reasons that support the valid existence of a difference in prevalences. Females may have increased biological vulnerability for depression. Cortisol levels appear higher in women, and women have higher glucocorticoid and mineralocorticoid receptor mRNA expression than men in the temporal lobe and prefrontal cortex. Furthermore, there is a close functional relationship between the HPA-axis and female sex hormones [6]. Although the exact mechanism by which sex hormones are involved in mood disorders remains to be sorted out, it is noteworthy that the prevalence of major depression increases in women during reproductive years, especially at times when sex hormone levels show rapid fluctuations, such as in the premenstrual, antepartum and postpartum periods, and during the transition to menopause [6]. The difference in prevalence between men and women may also be impacted by differential exposures to chronic psychosocial stress. Indeed, women's reproductive years - including associated transition periods such as puberty, pregnancy and early motherhood and menopause - are times of fluctuating gender-based psychosocial stressors as well as fluctuating sex hormones. At the population level, the most significant risk factors for depression are social, and include factors such as poverty, low socioeconomic status, lack of social support, life stress and exposure to domestic violence [3]. These risk factors are highly gendered; compared with men, women around the world tend to experience more socioeconomic disadvantages, more barriers to access to resources, explicit and systemic types of gender-based discrimination and victimization through gender-based violence [150]. Despite advances in the status of women, restrictive sociocultural ideas and expectations about gender remain. These can take a very real toll on the emotional stability of girls and women. These societal issues also carry practical, daily-life implications; for example, the increase in women working outside of the home has not been followed by a proportionate increase in men taking a greater corresponding role in housework and childcare. This situation has led to stress overload for many women, who are left juggling multiple demands [152]. The psychosocial stress stemming from the various social risk factors faced disproportionately by women, together with the biological vulnerabilities highlighted above, likely make occurrences of HPA-axis deregulation more common among

women. Exploration of the question of why women appear to have a higher prevalence of depression than men thus illustrates how stress and HPA-axis physiology appear to bridge the social and biological realms in understanding mental health.

The HPA-axis and monoaminergic systems

As detailed earlier in this paper, the monoamine theory of depression suggests that a decrease or deficiency in brain monoaminergic activity (notably for serotonin and norepinephrine) results in depression. Monoaminergic systems appear to be closely linked with the HPA-axis.

It has been found that cortisol (a primary end-product of HPA-axis activation) induces an increase in the expression of the gene coding for the serotonin transporter, which is involved in the uptake of serotonin from the synapse. This results in a decrease of serotonin available at the synapse [155]. Moreover, glucocorticoids also decrease the brain isoform of tryptophan hydroxylase (TPH 2) involved in the conversion of tryptophan to 5-OH-tryptophan; this also causes a reduction in serotonin. Furthermore, glucocorticoids augment the alternative pathway for tryptophan, catalyzed by indoleamine 2,3-dioxygenase (IDO), to produce excess quinolinic acid (QUIN), a neurotoxin [156,157], as reviewed by Herbert [35] and as discussed later in this paper. Glucocorticoids have also been implicated in various studies for downregulating and desensitizing serotonin receptors in the hippocampus, which, as already detailed, is a brain structure strongly implicated in depression (reviews by Joca and colleagues [84] and Flugge [158]). Furthermore, pro-inflammatory cytokines, that arise due to HPA-axis hyperactivation, attenuate monoamine levels, as discussed later in this paper.

Apart from glucocorticoids, CRH has been shown to play a role vis-à-vis 5-HT. Elevated CRH levels at extrahypothalamic sites in MDD may have potential consequences on serotonergic neurotransmission. Several reports have highlighted the importance of the possible interaction between CRH and 5-HT in the stress response (review by Anisman and colleagues [159]). In rats, chronic elevation of brain CRH results in decreased responsiveness of hippocampal 5-HT to stress [160]. In contrast, the stress-induced rise in hippocampal 5-HT is augmented in mutant mice deficient in CRH receptor type 1 (CRH-R1) [161]. Similarly, an acute intracerebroventricular administration of CRH in rats has been shown to result in a dose-dependent increase in the levels of hippocampal 5-HT and its metabolite, 5-hydroxyindoleacetic acid, suggesting the involvement of CRH-R1 [162]. Lastly, Oshima and colleagues [163] have reported alterations in hippocampal serotonergic neurotransmission in rats treated chronically with NBI 30775,

a CRH-R1 antagonist, which has antidepressant action. A molecular mechanism by which CRH and 5-HT might interact has been proposed recently by Magalhaes and colleagues [164]. Using cell cultures of both HEK293 and mouse cortical neurons, these authors have demonstrated that activation of CRH-R1 also increased 5-HT signalling by increasing the number of 5-HT₂ receptors at the cell surface. The increased serotonin signalling by CRH required CRH-stimulated internalization and recycling of CRH-R1 from endosomes, which also resulted in increased cell surface expression of 5-HT₂ receptors. The process likely involves heterologous dimerization of two receptor types in the endosomes, facilitating their recycling to the cell surface [164].

Just as the HPA-axis can affect monoaminergic activity, the reverse is also believed to be true. Hypothalamic 5-HT_{1A} receptors have been implicated in the release of hypothalamic CRH [165]. Selective serotonin reuptake inhibitor (SSRI) antidepressants are believed to attenuate hyperactivity of the HPA-axis via desensitization of these receptors [8] – an observation consistent with the “modern” monoamine theory of depression, which, as already mentioned, suggests that hypersensitivity of inhibitory monoaminergic auto- and heteroreceptors, located in certain brain regions, results in depression. The 5-HT_{3A} receptors have also been shown to have a regulatory role in HPA-axis activity, including potential interaction with CRH in the amygdala, further supporting the link between the HPA-axis and the monoamine systems [166].

The HPA-axis and pro-inflammatory immune function

Normal activation of the HPA-axis results in immune suppression; however, continuous hyperactivity of the HPA-axis results in an abnormal immune response. In patients with depression, glucocorticoid receptors on immune cells are believed to be hypofunctional, and, as a result, the glucocorticoids fail to suppress components of cellular immunity (review of evidence by Leonard [47]). This concept is supported by clinical evidence; it has been found that receptor sensitivity returns to normal following effective treatment [47]. Notably, prolonged elevation of glucocorticoids is believed to lead to desensitization of glucocorticoid receptors located on immune cells such as macrophages. Macrophages in the periphery and in the brain appear to be activated in depression to release pro-inflammatory cytokines, as discussed earlier in this paper. As highlighted below, pro-inflammatory cytokines can impact both brain structural integrity and monoaminergic neurotransmission. Thus, they explain many symptoms associated with depression. This observation is at the root of the macro-

phage theory/cytokine hypothesis of depression discussed earlier [47,48,50,51].

Therefore, an increase in pro-inflammatory cytokines is a key consequence of HPA-axis hyperactivity. However, some of the pro-inflammatory cytokines are in fact themselves potent activators of the HPA-axis, thereby increasing secretion of glucocorticoids [46,49,167]. TNF- α , IL-1 and IL-6 are, in particular, heavily involved in HPA-axis stimulation [168-170]. Furthermore, cytokines have also been implicated as mediating the loss of HPA-axis negative feedback mechanisms that occurs in depression, yielding hyperactivity (evidence reviewed by Schiepers, and colleagues [50]). Thus, the association between the HPA-axis and pro-inflammatory immune function appears to be potentially bidirectional.

The impact of pro-inflammatory immune function on monoaminergic systems

Pro-inflammatory cytokines can attenuate monoamine levels in the brain. Experimental evidence shows that IL-1 can activate the serotonin transporter, resulting in an increase in the reuptake of serotonin from the synaptic cleft [171]. Studies have also indicated that increased levels of acute phase proteins, which are elevated by IL-1 and IL-6, are linked with decreased levels of plasma tryptophan, which is the precursor of serotonin [172]. Cytokines such as interferon(IFN)- γ also result in depletion of tryptophan, via activation of the enzyme IDO, which accelerates tryptophan degradation [173]. Receptors for IL-1 have been identified on serotonergic neurons, and IL-1 also alters central noradrenergic system function [47]. These observations frame the overlap between the macrophage theory (cytokine hypothesis) and the monoamine theory of depression.

The HPA-axis and the structural integrity of brain regions

Glucocorticoid receptors have been found in multiple brain regions relevant to cognition and mood regulation – notably the hippocampus, the amygdala and the prefrontal cortex. Glucocorticoids sustained at high levels over long periods of time might induce toxic effects on the neuronal circuits in these regions [174,175]. This may explain stress effects on cognition, memory and emotion [84]. The hippocampus has proven, in recent studies, to be of particular interest. It has the highest density of receptors for corticosteroids within the brain, and is involved in the brain's response to stress and in HPA-axis activity regulation through its regulation of hypothalamic release of CRH [82-85].

Human imaging studies have implicated structural hippocampal changes in the pathophysiology of MDD (reviews by McEwen [80], Dranovsky and Hen [83]). Prolonged exposure to psychosocial stress is believed to promote glucocorticoid-dependent reduction in hippocampal volume, dendritic arborization and neurogenesis (i.e., proliferation of new cells); the evidence for the impact of stress on neurogenesis, both in animals and in adult humans, has been summarized in detail in a recent review by Lucassen and colleagues [176]. Stress-induced morphological damage to the hippocampus is believed to be rooted in a corticoid-dependent local increase of glutamate, which acts on *N*-methyl-D-aspartate (NMDA) receptors to evoke the release of nitric oxide, which has neurotoxic effects (review of evidence by McEwen [80], Sapolsky [175], Dranovsky and Hen [83] and Joca and colleagues [84]). Apart from resulting in a decrease in neurogenesis, stress also impacts the structure of mature neurons [84,175]. Furthermore, stress induces a decrease in levels of BDNF and other neurotrophic/growth factors, which are believed to play a role in neurogenesis, synaptic morphology and membrane excitability changes. This leads to alterations of synaptic transmission, connectivity and function in the hippocampus [84,175]. Finally, via its effects on the serotonergic system, glucocorticoids cause a shift away from the serotonin-producing tryptophan pathway, to an alternate pathway for tryptophan, catalyzed by IDO, which produces excess QUIN. Increased QUIN production may cause excess stimulation of NMDA receptors, yielding neurotoxicity [156,157] (review by Herbert [35]).

Hypercortisolism in depression is also believed to inhibit prefrontal cortex activity and metabolism. This is consistent with postmortem studies that show morphological changes in the prefrontal cortex in major depressive disorder [6,86].

While hyperactivity of the HPA-axis is believed to lead to brain damage, the reverse is also believed to occur. Both the hippocampus and the prefrontal cortex, for example, provide regulatory inhibition of the HPA-axis. Lesions that disrupt this ability, via loss of the corticosteroid receptors that mediate negative feedback, are thus associated with hypercortisolism and depression [6]. There appears to be a potentially two-way interaction between HPA-axis activation and the structural integrity of relevant regions of the brain.

The impact of pro-inflammatory immune function on the structural integrity of brain regions

Cytokines induce activation of the enzyme IDO, which causes increased production of neurotoxic metabolites of the kynurenine pathway, such as 3-hydroxy-kynurenine (KYN) and QUIN [177], leading to hippocampal damage [178]. Pro-

inflammatory cytokines are also believed to inhibit hippocampal neurogenesis – which links with the observation that hippocampal volume is decreased in long-term depression [46,49].

Monoaminergic systems and the structural integrity of brain regions

Neurotransmission requires structurally-intact neurons and receptors. Neurons that are damaged and/or reduced in number, as well as desensitized or downregulated receptors, will impair neurotransmission. Thus, structural integrity directly impacts monoaminergic neurotransmission. The reverse has also been demonstrated. Monoamines are involved in the regulation of hippocampal neurogenesis, and in the release of neurotrophic factors. Lines of experimental evidence to this end include studies that show that antidepressant medications increase neurogenesis, in part through increase in BDNF and other neurotrophic factors (review by Duman and Monteggia [87]). Evidence also stems from other studies showing that lesions that damage monoaminergic neurons impede neurogenesis, and also from additional work looking at the roles of monoaminergic receptors, notably 5-HT_{1A} receptors. These studies have been reviewed in detail elsewhere [83,84]. Based on this idea, antidepressants may be thought to act by reversing the effect of stress on neurogenesis [83,84].

Discussion and Conclusions

George Engel, pioneer of the biopsychosocial model of health, heavily criticized the traditional biomedical model's over-reductionist approach to health and medicine in his seminal 1977 paper "The Need for a New Medical Model: A Challenge for Biomedicine". He argued that "concentration on the biomedical and exclusion of the psychosocial distorts perspectives and even interferes with patient care" (p. 131) [179]. He had equally pointed criticisms for those in psychiatry who sought to deny or minimize the biological components of mental health; for example, Thomas Szasz, who, in his famous 1960 paper, suggested that mental illness is a "myth" [180]. Engel advocated for the rejection of the mind-body dualism at the heart of both of the above polarized viewpoints. Instead, he encouraged a systems-oriented approach to understanding both physical and mental health, in recognition of the complex interactions between determinants that stem from levels ranging from molecular to societal [179]. Despite the popularity of the biopsychosocial model in the more than 30 years since Engel's first paper – and despite the increasing interest in interdisciplinary approaches to health research and practice – mechanistic discussions of depression in the literature remain

fairly segregated along traditional disciplinary lines. This is true not just in between biological and psychosocial “camps”, but also within them. The latter is apparent in examining the biological psychiatry literature.

The depiction, in Figure 1, of a proposed framework incorporating the major physiological theories of depression includes bidirectional arrows between almost all of the key physiological systems implicated in depression. This may suggest the occurrence of positive-feedback loops leading to increased deregulation and damage. Indeed, the apparent two-way association between the HPA-axis and the hippocampus structure, for example, led to the proposal of a “glucocorticoid cascade hypothesis” in which hippocampal damage is believed to disinhibit HPA-axis negative-feedback mechanisms, resulting in repetitive hypersecretion of cortisol and further damage in the hippocampus [181]. Experiments to confirm this hypothesis have provided mixed results (discussed by Swaab and colleagues [6]). In general, further targeted bench research is required before a positive-feedback phenomenon can be definitively declared in regards to any of the associations discussed. Furthermore, while this paper has focussed on the integrative potential of the HPA-axis, it is recognized that the aetiology of depression is complex, and that other important pathways and mechanisms may be involved. These other pathways include those that potentially link biological, psychological and social determinants of health with depression pathophysiology, without direct or explicit involvement of psychosocial stress and HPA-axis activation. Such pathways include those mediated or moderated by injuries and chronic health conditions, which are comorbid to depression via shared physiology, as well as diet and nutritional status. What can be hypothesized overall is that a better understanding of the multiple systems involved, and of the directional complexity of the apparent associations between them, may help to explain the wide-ranging symptoms associated with major depressive disorder, and the wide variety of medical conditions for which there are associations of comorbidity. Comorbid disorders include migraine headaches, cardiovascular disease, disorders involving chronic inflammation (e.g., rheumatoid arthritis, allergies, Alzheimer’s disease, multiple sclerosis, etc.), thyroid disorders, Cushing’s Syndrome, esthesioneuroblastoma, hypertension, stroke, type 2 diabetes and head injuries; all of these disorders appear to share pathophysiological pathways with depression [6,45,46, 69-72, 117, 182]. Furthermore, untangling the physiological complexity involved may also perhaps contribute to accounting for and addressing the challenges in treating depression effectively, the diversity in symptoms and treatment outcomes among individual patients, and the high

rate of symptom persistence and relapse. Further research is warranted to gain a more comprehensive and contextualized understanding of these interweaving associations.

HPA-axis deregulation appears to be the key player not only in the bridge between the broader biological and psychosocial camps in psychology, but also between the various theories and mechanisms proposed in the realm of biological psychiatry. From a diagnostic perspective, this may offer opportunities for the application of biomarkers for biological vulnerability and early detection; however, there are more upstream implications, as well. Taken together, the efforts of integration presented point to the destructive and extensive impact of chronic life stress on physiological systems implicated not just in depression, but in a wide range of physical and mental disorders. Furthermore, they also highlight the artificiality of the academic boundary often placed between the bench sciences and the social sciences when studying human health.

This paper was born out of the authors’ quest for an integrated framework to understand depression mechanisms, after noting the prominent role and transcending appearance of psychosocial stress in the biological, psychological, sociological and epidemiological literature on depression. As part of this broad quest, one of the three objectives of this paper was to sort out the links between the diverse biological mechanisms proposed in the biological literature on depression, after noting that all of the systems appear to involve the HPA-axis. To achieve this particular objective, a significant amount of page space has had to be devoted to discussion of biological mechanisms and their overlap. This allocation of space should not, however, be interpreted to imply that biological mechanisms are more important. Because biological mechanisms are more downstream, and therefore are more immediate to symptom presentation, they have received more attention in medical literature. Upstream factors, however, hold the key to early intervention and prevention; the unifying framework proposed in this paper demonstrates that the upstream factors to target in this regard are predominantly psychosocial in nature. From among those psychosocial factors, the importance of societal factors becomes especially apparent when one moves away from an individual-level understanding of health, to an understanding of health at the population level. The World Health Organization’s recent report on the social determinants of population health corroborates the population-level social gradient of health that can be noted for virtually all disorders, including depression –that strata of the population experiencing greater social disadvantage also experience poorer health [150]. It is generally recognized that social disadvantage can affect the ability of individuals to access health care and other health-

impacting services and resources, and the ability to participate in health-promoting behaviour such as consumption of a healthy diet and conduction of regular exercise [150]. These issues ultimately can have pathophysiological ramifications. A fact that is surprisingly underemphasized in current discussions on the social determinants of health is that the chronic psychosocial stress caused by social factors is, in and of itself, capable of unleashing pathophysiology that can contribute to various disorders, including depression. Clinical approaches presently in place for depression are designed primarily to attempt to treat or moderate pathophysiology in individuals once it is underway; these include both pharmaceutical approaches, and psychotherapeutic approaches. Primary prevention of depression as a population health issue, however, lies in effectively addressing the predominantly social causes of one of depression's most significant risk factors: chronic psychosocial stress.

List of Abbreviations

ACTH	adrenocorticotrophic hormone
ADH	antidiuretic hormone
BDNF	brain derived neurotrophic factor
COMT	catechol- <i>O</i> -methyltransferase
CRH	corticotrophin releasing hormone
DRN	dorsal raphe nucleus
DSM	Diagnostic and Statistical Manual of Mental Disorders
FGF	fibroblast growth factor
HPA	hypothalamic-pituitary-adrenal
5-HT	5-hydroxytryptamine
IDO	indoleamine-2,3-dioxygenase
IFN	interferon
IL	interleukin
IGF	insulin-like growth factor
KYN	3-hydroxy-kynurenine
MAO	monoamine oxidase
MDD	major depressive disorder
MRN	median raphe nucleus
NGF	nerve growth factor
NMDA	N-methyl-D-aspartate
NT	neurotrophin
QUIN	quinolinic acid
SSRI	selective serotonin reuptake inhibitor
SNP	single nucleotide polymorphism
TNF	tumour necrosis factor
VEGF	vascular endothelial growth factor

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