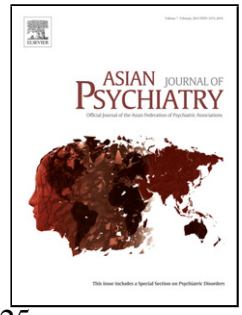

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PII: S1876-2018(16)30319-7
DOI: http://dx.doi.org/doi:10.1016/j.ajp.2017.01.025
Reference: AJP 1045

To appear in:

Received date: 18-7-2016
Revised date: 18-1-2017
Accepted date: 21-1-2017

Please cite this article as: Dean, Jason, Keshavan, Matcheri, The Neurobiology of Depression: an Integrated View.Asian Journal of Psychiatry http://dx.doi.org/10.1016/j.ajp.2017.01.025

The Neurobiology of Depression: an Integrated View

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Highlights

- Depressive disorders may represent an interactive matrix of reciprocally interactive pathophysiological mechanisms
- These biological mechanisms may reduce neuroplasticity and compromise the functional integrity of affect regulation neurocircuitry
- An R-Doc approach to depressive disorders is essential to understand each biological mechanism before understanding their interaction
- An overly reductionistic approach may miss the essence of the disorder, which likely lies in the complex interactions among various pathophysiological mechanisms, rather than in one mechanism in isolation
- An integrated view of the neurobiology of depression is only one hypothesis, and depressive disorders may represent several subsyndromes, or even numerous discrete disorders

ABSTRACT

Major Depressive Disorder (MDD) is one of the most common and debilitating mental disorders; however its etiology remains unclear. This paper aims to summarize the major neurobiological underpinnings of depression, synthesizing the findings into a comprehensive integrated view. A literature review was conducted using Pubmed. Search terms included "depression" or “MDD” AND "biology," "neurobiology," "inflammation," "neurogenesis," "monoamine," and "stress." Articles from 1995-2016 were reviewed with a focus on the connection between different biological and psychological models. Some possible pathophysiological mechanisms of depression include altered neurotransmission, HPA axis abnormalities involved in chronic stress, inflammation, reduced neuroplasticity, and network dysfunction. All of these proposed mechanisms are integrally related and interact bidirectionally. In addition, psychological factors have been shown to have a direct effect on neurodevelopment, causing a biological predisposition to depression, while biological factors can lead to psychological pathology as well. The authors suggest that while it is possible that there are several different endophenotypes of depression with distinct pathophysiological mechanisms, it may be helpful to think of depression as one united syndrome, in which these mechanisms interact as nodes in a matrix. Depressive disorders are considered in the context of the RDoC paradigm, identifying the pathological mechanisms at every translational level, with a focus on how these mechanisms interact. Finally, future directions of research are identified.

Key words: Depression; biology; neurobiology; MDD; inflammation; neurogenesis; serotonin; psychology; stress; attachment

INTRODUCTION

Major depressive disorder (MDD) is one of the most prevalent and debilitating psychiatric disorders. In 2014, 7% of Americans over the age of 12 reported depression within the past two weeks (Center for Disease Control and Prevention, 2014) and in 2003 the World Health Organization estimated a global lifetime prevalence of roughly 16% (World Health Organization, 2003). Characterized by impairments in cognition, emotional regulation, memory, motoric function, motivation, and neurovegetative symptoms, MDD can cause severe disability. In addition to its primary effects, the disorder also causes secondary disability, as patients with depression are more likely to develop chronic medical illnesses, and depressed patients are less likely to comply with medical treatment (World Health Organization, 2003). The combination of the primary disability caused by depression and the secondary disability of chronic medical illness makes MDD one of the most costly medical burdens in the world. The economic burden of MDD in the United States in the year 2000 was estimated to be 83.1 billion dollars, with 26.1 billion dollars (31%) directly related to medical costs, 5.4 billion dollars (7%) related to suicide, and 51.5 billion dollars (62%) due to workplace costs including absenteeism and reduced productivity (Greenberg et al., 2003).

Despite tremendous progress in neuroscience research over the past few decades, the pathophysiology of MDD has not been fully elucidated. Research has implicated several mechanisms including altered serotonergic, noradrenergic, dopaminergic, and glutamatergic systems, increased inflammation, HPA axis abnormalities, vascular changes, and decreased neurogenesis and neuroplasticity. However, these findings are not present in every patient, and treatments that target these mechanisms directly have only partially been explored. While the various biological mechanisms implicated in depression may appear unrelated, indicating that MDD may actually represent several biologically discrete illnesses, research has

shown that all of these pathways are related and interconnected. A unified theory of depression that incorporates all of these biological mechanisms would be helpful in several ways. First, an overly reductionistic approach that focuses on discrete biological pathways without recognizing the ways in which they interact risks missing the true nature of the illness. Second, this model could explain the significant heterogeneity found in depressed patients; only a fraction of patients with MDD exhibit each specific finding. Third, this framework would provide new research directions that would focus on understanding the complex interaction among these pathophysiological factors, rather than focusing on the factors in isolation.

This paper will suggest a unified theory of depression that conceptualizes the condition as resulting from an interactive matrix of pathophysiological mechanisms. An alteration in the matrix at any one node has the ability to trigger the entire cascade of biological effects. As such, focusing on one biological factor in isolation may totally miss the true nature of depression as an illness in which these different factors interact and stimulate each other. Too narrow a focus risks mistaking a single part of a much larger process as the cause of the illness itself. We wish to stress that this unified theory of depression is only one hypothesis among several possibilities. It is also possible that depressive disorders may represent several subsyndromes or even numerous discrete disorders.

It is helpful to organize MDD according to its etiology, pathophysiology, and expression. MDD is an exceedingly complex disorder, with several etiologies including genetic, epigenetic, and environmental factors, which together lead to the development of the disorder. The disorder itself has several pathophysiological mechanisms, which can be organized according to the level of neurochemistry, tissue and organ-level pathology such as inflammation or an increased stress response, and altered neurocircuitry. Finally, the disorder has numerous phenotypic expressions,

including depressive ideation, depressive affect, motor symptoms,
and neurovegetative symptoms which highly overlap between several diagnostic entities, making categorical symptom-based distinctions problematic for the purpose of discovering pathophysiological substrates. For this reason, investigating pathophyisiological domains across translational units of analyses (i.e. molecular, cellular, neurocircuitry, and behavioral levels) may be more fruitful than research based on the DSM categorical diagnosis. The recently formulated Research Domain Criteria (RDOC) paradigm (Insel and Cuthbert) emphasizes the analysis of each particular expression of a disorder, such as negative salience, according to each translational level. This paper will follow the RDOC paradigm by discussing these different levels and their interactions in the production of a depressive phenotype.

A discussion of the etiology or expression of MDD is beyond the scope of this paper. Rather, this paper will focus specifically on pathophysiology, showing that the various pathophysiological mechanisms at every level can be understood as an interactive matrix. Whereas an understanding of etiology is important for prevention, an understanding of pathophysiology is most pertinent to treatment, as the different treatment modalities target different pathophysiological mechanisms.

Progress in this field has been hampered by the fact that there are several schools of thought regarding the pathophysiology of depression that are often at odds with each other. There is an ancient Indian parable of six blind men attempting to describe an elephant. Unable to see the giant animal as a whole, each describes the elephant according to what he feels with his hands, as either a tree trunk, a wall, and so on. In a sense, MDD, and perhaps every psychiatric disorder, is like the proverbial elephant. If we make the mistake of equating one small part of a larger process with the disease itself, we run the risk of missing the big picture, which is that

most psychiatric disorders probably represent an interactional matrix of many factors, and cannot be reduced to those factors alone.

The literature on the biological basis of depression is vast. As this paper attempts to create an integrated framework in which multiple biological theories are synthesized, an emphasis was placed on papers that focused on an interaction between disparate biological systems. A literature review was conducted using Pubmed, with search terms including the term "depression" coupled with the following search terms: "biology," "neurobiology," "inflammation," "neurogenesis," "monoamine," and "stress." Articles from 1995-2016 were reviewed with a focus on the connection between different biological and psychological models of depression. A Pubmed search of the terms “biology” and “depression” from 1995-2016 returns 5,096 articles. A more limited search including the term “monoamine,” for instance, returns only 95 articles. Thus a series of more specific searches using the above terms made the review process more manageable. Articles were selected for their relevance to an understanding of the pathophysiology of depression, and many articles were excluded due to their lack of direct relevance to the topic or lack of generalizability. Finally, several important articles that the authors wished to include, but had been missed by the Pubmed search, were added for their heuristic utility based on the authors’ own knowledge of the literature. A total of 66 papers are included here. The distinction between the pathophysiology of MDD and bipolar depresion is beyond the scope of this paper and was not included in our review or discussion. For details, the reader is referred to other recent reviews (Brady et al, 2014; Brady and Keshavan, 2015).

MONOAMINE NEUROTRANSMISSION

A major hypothesis for the pathophysiology of depression, the monoamine hypothesis, posits that depression is caused by an alteration in levels of one or more of the monoamines, including serotonin (5-HT), norepinephrine (NE) and dopamine (DA). Evidence for the serotonergic theory includes the finding that serotonin metabolites are reduced in patients diagnosed with MDD and that antidepressants such as tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors have been shown to increase levels of serotonin in the brain. Furthermore, chronic antidepressant treatment has been shown to down-regulate inhibitory presynaptic 5-HT1A somatodendritic autoreceptors. As these presynaptic autoreceptors inhibit 5-HT release, their down-regulation increases the probability of 5-HT release, which has been associated with antidepressant response (Richelson, 2001). Similarly, depletion of tryptophan, an essential amino acid needed for 5-HT synthesis, has been shown to induce depressive symptoms in patients who were successfully treated for depression with an antidepressant, though tryptophan depletion had no effect on untreated depressed patients. These findings imply that increased serotonin levels are necessary for antidepressant medication effects, though depletion of serotonin alone may not be sufficient to cause depressive symptoms (Bell, Abrams, and Nutt, 2001). In addition, genetic abnormalities in serotonergic transmission have been linked to depression. For instance, the serotonin-linked polymorphic region (5-HTTLPR), is a degenerate repeat in the gene that encodes the serotonin transporter (SLC6A4). The s/s genotype of this region is associated with a reduction in serotonin expression, associated with increased vulnerability to depression (Caspi et al., 2010), though there is some controversy on this topic (Fabbri, 2013). Similarly, the G(-1019) variant of the Htr1A promoter region which controls expression of the 5-HT1A autoreceptor is associated

with reduced 5-HT1A receptor expression. Both these polymorphisms have been associated with impaired affective regulation and depressive symptoms (Caspi et al., 2010).

NE is also involved in mood regulation, as evidenced by the fact that medications that inhibit NE reuptake, such as TCA's, SNRI's, and NDRI's, and those that increase NE secretion, such as mirtazapine, are effective antidepressants (Leonard, 2001). Chronic stress is thought to alter the noradrenergic system, which is integrally related to the neuroendocrine and immune systems. For instance, chronic stress leads to an increase in the activity of tyrosine hydroxylase, the enzyme involved in NE synthesis, in the locus ceruleus. Stress also stimulates the production and release of NE by causing the increased secretion of corticotropin-releasing factor (CRF) from the hypothalamus, which in turn triggers the release of ACTH from the pituitary gland, which subsequently stimulates the adrenal gland to release NE and cortisol (Leonard, 2001). Increased levels of cortisol and NE subsequently increase sympathetic drive and the release of cytokines, which have been shown to have reciprocal effects on the HPA axis, as well as neurotoxic effects, as discussed below.

The mesolimbic pathway, consisting of dopaminergic neurons originating in the ventral tegmental area and projecting to the nucleus accumbens, mediates the reward pathway and motivation. There are several lines of evidence that implicate altered dopaminergic transmission and the mesolimbic pathway in the pathophysiology of depression. These include the fact that some neurovegetative symptoms of depression, including anhedonia and reduced motivation, are related to a malfunctioning of the reward system, as well as the recognition that primary neurological disorders of dopamine production, such as Parkinson's Disease, can cause depression. Finally, the fact that antidepressant agents such as bupropion increase dopamine levels in the brain provides indirect evidence for the role of dopamine in mood regulation. Watt

and Panksepp (Watt and Panksepp, 2009) have conceptualized depression as a disorder of the mesolimbic system, in which an individual who has undergone significant stress or loss develops a shutdown of the reward pathway, which is experienced as anhedonia and despair. In line with this theory, studies have shown that chronic stress causes neuroadaptive changes in the dopaminergic mesolimbic pathway, and that these changes are involved in altered expression of brain-derived neurotrophic factor (BDNF) and neuroplasticity (Nestler and Carlezon, 2006).

Serotonin, NE, and dopamine are all interrelated and effect each other's concentrations in the brain. For instance, dopamine has been shown to have an inhibitory effect on the release of NE from the locus ceruleus, while NE has a excitatory and inhibitory effect on dopamine release in the ventral tegmental area, through stimulation of α-1 and α-2 receptors respectively. Both NE and dopamine increase serotonin release from the dorsal raphe nucleus through α-1 and D-2 receptors, respectively. These findings indicate that the monoamine neurotransmitters do not operate in isolation, but rather that these neurotransmitter systems are integrally interconnected. An alteration in one of these neurotransmitters likely effects the function of the other two (El Mansari et al, 2010).

Gluatamate has also been implicated in mood regulation. The fact that ketamine, an NMDA receptor antagonist, acts as a potent and fast acting antidepressant has led to great interest in the glutamatergic system as a possible target for antidepressant treatment. Clinical studies have shown that ketamine leads to a rapid antidepressant effect, occurring in hours, rather than weeks, as is the case with traditional antidepressants (Machado-Vieira R, Henter ID, Zarate CA Jr., 2015). Ketamine has been hypothesized to act through the antagonism of NMDA receptors in GABA-ergic interneurons, which reduces inhibition of glutamate release in glutamatergic neurons. This disinhibition leads to a glutamate surge, with glutamate

subsequently selectively binding to AMPA receptors. Increased stimulation of AMPA receptors leads to several second messenger cascades, including eEF2k inhibition, GSK-3 inhibition, and mTOR activation, all of which lead to increased neuroplasticity. Ketamine has also been shown to increase the release of BDNF in hippocampal pyramidal neurons, which increases neuroplasticity as well (Iadarola et al, 2015). These findings imply that glutamate may be involved in mood regulation, possibly through the maintenance of neuroplasticity.

HPA AXIS DYSREGULATION AND THE STRESS RESPONSE

Stress and depression are often related. For instance, stressful life events can precipitate depressive episodes in vulnerable individuals (Kendler, Karkowski, and Prescott, 1999), and childhood stress in the form of abuse or neglect increases the risk of depression later in life (Pechtel and Pizzagalli, 2011). Animal models have shown that chronic mild stress induces a spectrum of behavioral abnormalities in rodents that parallel depressive symptoms including decreased sucrose intake and mating (anhedonia), decreased motivation, reduced grooming, and sleep changes (Willner, 2005). In recent decades, several abnormalities in the HPA axis associated with a hyperactive response to stress have been found in depressed patients. Some of these alterations include hypersecretion of CRF from the paraventricular nucleus of the hypothalamus, impaired negative feedback of the HPA axis, enlarged adrenal glands, hypercortisolemia, and decreased suppression of cortisol in response to dexamethasone (Pruessner et al., 2003). In a subset of depressed patients, a hypersensitive HPA axis results in cortisol release in response to lower levels of stress as well as chronically elevated cortisol levels.

What are the neurobiological ramifications of elevated cortisol levels in the brain? Studies on the effects of glucocorticoids have elucidated some mechanisms which may explain the depressive consequences of hypercortisolemia. Three brain areas that have been shown to be altered by increased glucocorticoids are the medial prefrontal cortex (mPFC), the hippocampus, and the amygdala. The mPFC is involved in executive functioning and the processing of emotion, the hippocampus is involved in memory and learning, and the amygdala is involved in emotion processing. Chronic stress has been shown to decrease the dendritic complexity of pyramidal neurons and increase the transcriptional activity of GABA interneurons in the mPFC, decreasing activity in this area (Cerqueira et al., 2005). As the mPFC is implicated in the cognitive processing of emotions generated by subcortical regions such as the amygdala, reduced activity in this area leads to inadequate processing of negative affect. Furthermore, increased cortisol levels impair the ability of the hippocampus to adapt to a changing environment. Chronically stressed animals exhibit reduced plasticity and long-term potentiation in CA1 hippocampal neurons mediated by the glucocorticoid receptor (GR) (Alfarez, Wiegert, and Krugers, 2002), leading to impaired adaptation and learning.

In addition to the above cellular changes, high levels of cortisol also alter functional connections in the brain that deal with the processing of emotion and adaptation. For instance, chronic stress decreases long-term potentiation in the projections from the basolateral amygdala to the mPFC and increases excitability in the amygdala in response to stress, resulting in increased reactivity to stress and decreased cognitive processing (Duvarci, 2007). Chronic stress also shifts functional memory from hippocampal-based learning to habitual striatum-based learning, as MR-mediated glucocorticoid effects cause an uncoupling of the amygdala from the hippocampus and increased connectivity to the striatum (Schwabe et al., 2013). Taken

together, glucocorticoids affect synaptic changes and higher level alterations in emotional-cognitive circuitry that shifts an organism from adaptive contextual learning and exploration to habitual learning. In health, this mechanism allows an organism to avoid exploration during chronic stress, relying on habit to safely navigate external threats. However, when the external environment is misinterpreted as dangerous, this shift away from adaptive learning may happen inappropriately, leading to disinterest in the external world, internal focus, and depressive symptoms (Myers, McKlveen, Herman, 2014).

The Diathesis-Stress Model provides a neurological basis for a link between chronic psychological stressors and depression. This model views depression and many other psychiatric disorders as developmental derailments that evolve over time. A diathesis is a predisposition, which could be either biological or psychological. In this conception, depression is not caused by one biological or psychological factor in isolation. Rather, in a vulnerable patient who is predisposed to a negative response to stress, repeated stressors can cause that pre-existing vulnerability to manifest itself. One example of this idea would be the genetic polymorphisms in the serotonin transporter gene mentioned above. Individuals with the s/s genotype of this polymorphism have been shown to react more to stressful situations and to have increased rates of depression. This diathesis or genetic predisposition is not sufficient to cause depression itself until it is brought out by environmental stressors (Beck, 2008; Scher, Ingram, and Segal, 2005). It is the combination of stressors and a pre-existing vulnerability, of nature and nurture, that causes disorder. The HPA axis may provide a biological basis for this process, in which early stress leads to a functional “hyperactivation” of the HPA axis and a predisposition towards a maladaptive reaction to stress, rather than depressive symptoms themselves. This biological

diathesis is then brought out by an acute stressor, leading to the entire cascade of effects described above.

When the concept of "stress" is extended from objective external factors to internal psychological stress, the model of chronic stress causing depression lends itself to several psychological theories. In *Attachment and Loss* (1980), Bowlby presents his *Attachment Theory*, which focuses on the strong emotional bonds that animals and humans form as children with their caregivers and as adults with other adults. Enduring emotional bonds with attachment figures is important for social functioning of the individual, and as such is a very powerful motivation of human behavior. An undisturbed attachment provides a sense of safety, a threat to these relationships causes anxiety, reunion produces joy, and separation causes distress and sorrow. In order to maintain these relationships, animals and humans employ attachment behaviors, which could be as simple as checking for the attachment figure or involve following, clinging to, or calling for a caregiver. When an animal or human is separated from an important attachment figure, significant distress ensues, and the individual employs attachment behaviors in an attempt to find the lost caregiver, which Bowlby terms a "protest." Over time, if the lost object is not found, this protest gradually diminishes until the individual "gives up." An important aspect of this theory is the concept that early loss may cause an individual to deviate developmentally to an insecure attachment type. These individuals may be hypersensitive to loss, greatly magnifying the psychological damage done by future losses (Bowbly, 1980). An inconsistent caregiver may elicit conflicted feelings from a child, leading to an insecure or anxious attachment style in which fear of abandonment is inextricably mixed with love for the attachment figure. In this framework, depression can occur in the following way. An individual is abandoned by a key attachment figure and experiences significant anger towards

this caregiver; however, due to an ambivalent relationship that combines both love and anger, the patient spares the loved object his anger and instead internalizes the object. This anger towards a beloved attachment figure generates guilt as well, and depression can be seen as self-punishment for feelings of forbidden anger (Holmes, 2013).

Otto Kernberg (2009) summarized the psychodynamic theory of depression, which conceptualizes depression as a response to the loss of an ideal state of self (Bibring, 1953) due to the loss of an internalized object (Freud, 1917) and the belief that one's own aggression has destroyed the good internalized object (Klein, 1940). This state is more common in patients with a biological predisposition, including temperament, hyperactive HPA axis, and biologically amplified affects of rage and panic, as well as a psychological predisposition, in which aggressive internalized object relations predominate over libidinal internalized images of self and other. Importantly, early deprivation and early life stress, including insecure early attachment, can cause HPA axis hyperactivity, as well as pathological internalized object relations (Kernberg, 2009).

Cognitive theory, originally conceptualized by Dr. Aaron Beck, views depression as resulting from pathological cognition. In a 2008 review, Beck summarized the developments in his theory and explained them in the context of growing biological research. The main premise of cognitive theory is that negative cognitive biases affect the way an individual perceives the external world. Early stress, loss, or trauma can lead to the development of negative cognitive schema which serve as a biased framework with which to interpret future events. The development of these negative biases confers a cognitive vulnerability to the patient, increasing the risk of developing depression in response to future stressors. In addition to cognitive vulnerability which predisposes a patient to a full-blown depressive episode, Beck attributes

milder acute depressive symptoms to cognitive reactivity. Cognitive reactivity denotes a negatively biased response to every-day stressors. Increased cognitive reactivity in depressed patients can lead to mild and transient depressive symptoms due to misinterpretation of everyday negative events. Furthermore, Beck discusses what he calls a depressive mode, which in addition to a "hub" of negative cognitive schema includes affective, motivational, behavioral, and physiological schemas. External events are interpreted via these negative cognitive schemas which then activate the other aspects of the depressive mode. Repeated activation of this mode eventually causes it to become fixed and act autonomously, causing the patient to ignore positive external stimuli and focus internally. This process leads to anhedonia, lack of motivation, increased rumination, and depression.

Beck (2008) proposes a neurobiological mechanism underlying what he calls the "depressive mode". Genetic polymorphisms in the 5-HT transporter (see above) have been shown to lead to increased reactivity of the amygdala, which leads to increased reactivity to negative events and a negative attentional bias. This attentional bias towards negative events leads to cognitive distortions such as personalization, overgeneralization, and exaggeration, which in turn lead to dysfunctional attitudes regarding personal worth and acceptability. Repeated activation of these attitudes ultimately creates negative cognitive schema, which in turn activate the HPA axis in response to the misinterpretation of external events (Beck, 2008).

In all of these psychological models, early life stress has a lasting effect on the HPA axis, causing a biologically determined sensitivity to later stressors, as well as pathological psychological factors that predispose to depressive affect. Similarly, recent research has shown that early life adversity leads to structural and functional changes in structures such as the uncinate fasciculus (Hanson JL et al, 2015), a white matter tract that connects the amygdala with

medial structures in the PFC that are involved in affect processing. Thus, psychological stress may lead to neurodevelopmental changes in affective processing circuits, creating a biological predisposition to depression in later life. These theories provide a powerful model towards the integration of biological and psychological models of depression.

INFLAMMATION

Increased levels of inflammatory markers such as IL-1β, IL-2, IL-6, TNF-α, CRP, and PGE2 have been found in patients with depression (Felger and Lotrich, 2013). Studies have also shown that inducing inflammation in research subjects causes depression. For instance, Wright et. al showed that subjects who were vaccinated with S. Typhi subsequently developed depressed mood in proportion to increased IL-6 levels (Wright et al., 2005). Similarly, INF-α treatment of Hepatitis C causes depressed cognition related to increased IL-2, IL-6, and TNF-α (Wichers et al., 2007). As psychological stress has been shown to increase the production of cytokines such as IL-1β, IL-6, and TNF-α (Steptoe, Hamer, and Chida, 2007), there exists a positive feedback between depression and inflammation in which inflammation causes depression and psychological stress, which in turn is pro-inflammatory.

The bidirectional relationship between depression and inflammation is paralleled by the clinical relationship between depression and inflammatory disorders. Depressed patients have an increased rate of autoimmune disorders, and there are higher rates of depression among patients with inflammatory diseases (Pasco et al., 2010). In addition, anti-inflammatory agents have been used successfully as adjuncts to antidepressants. For instance, anti-inflammatory treatment of psoriasis has been shown to reduce depressive symptoms independent of change in psoriasis symptoms (Tyring et al., 2006).

The depressive symptoms of anhedonia, fatigue, and internal focus caused by inflammation are often termed "sickness behaviors." The mechanism by which inflammation causes depression is actually thought to be an adaptive response to infection. Acute inflammatory illnesses and infections require a great deal of energy expenditure, and exploration, mating, and other activities can lead to a dangerous expenditure of energy. Therefore, it is adaptive for inflammation to cause anhedonia and fatigue, causing an organism to forego exploration and mating and to focus on healing. The problem with this mechanism, of course, is that it is only adaptive for acute illness. Chronic inflammatory conditions, which include chronic psychological stress, can lead to prolonged sickness behavior when it is no longer adaptive (Rosenblat et al., 2014).

It is worth stressing the overlap between inflammation and many of the most prevalent chronic illnesses. Metabolic Syndrome includes several conditions which are related to a proinflammatory state and vascular disease, including obesity, insulin resistance, hypertension, and dyslipidemia. Pro-inflammatory markers, such as TNF-alpha, IL-1, IL-2, and IL-6 may be elevated in patients with metabolic syndrome, which has recently been conceptualized as a neuroinflammatory disorder. Though the mechanism by which inflammatory molecules can induce metabolic syndrome remains unclear, one possible mechanism includes TNF-alpha leading to insulin resistance as well as altering the function of pro-opiomelanocortin and neuropeptide Y neurons, which inhibit and stimulate feeding, respectively (Singh et al., 2012). Inflammation may also predispose to vascular disease, which has been implicated in late-life depression. Late-life depression has been found to be associated with cognitive dysfunction and increased white matter hyperintensities on MRI, representing ischemic damage to white matter tracts. These findings have been conceptualized in a disconnection hypothesis in which

ischemic damage to the white matter is thought to lead to altered connection between affective and cognitive circuits. Increased inflammation and hypoperfusion of the white matter are thought to cause ischemic damage, causing alterations in the connections between different circuits (Taylor, Aizenstein, and Alexopoulos, 2013). As the components of metabolic syndrome such as obesity, diabetes, hypertension, and dyslipidemia can all lead to atherosclerosis, it is likely that these conditions could also cause or exacerbate depression through vascular white matter disease. The same concern would apply to other chronic inflammatory conditions as well, including coronary artery disease, chronic obstructive pulmonary disease, and rheumatologic disorders.

REDUCED NEUROGENESIS AND NEUROPLASTICITY

The brain possesses remarkable plasticity, able to rapidly create and eliminate synapses as well as to alter functional circuits in adaptation and learning. One of the molecular factors needed for healthy neuroplasticity is brain-derived neurotrophic factor (BDNF). BDNF is a neurotrophin that promotes the survival of existing neurons and encourages the growth and differentiation of new neurons and synapses (Acheson et al., 1995). The finding that serum levels of BDNF are reduced in patients diagnosed with MDD (Monteleone et al., 2008) implies a possible role of BDNF in the pathophysiology of depression. Furthermore, a knock-out experiment of BDNF in the dorsal dentate gyrus of the hippocampus was able to induce depressive behavior in rats (Taliaz et al., 2010) suggesting that reduced production of BDNF and neuroplasticity can lead to depression. In parallel, antidepressant effects have been shown to be associated with increased hippocampal neurogenesis (Santarelli et al., 2003). Fluoxetine has been shown to increase BDNF mRNA expression in the dentate gyrus of the hippocampus, the

ventral tegmental area (VTA), and the nucleus accumbens (Molteni et al., 2006). The VTA and the nucleus accumbens have been shown to be responsible for the reward circuit, which when altered can produce anhedonia in MDD, while the hippocampus is essential for memory. Taken together, these findings suggest that BDNF may be necessary for limbic and cortical circuits to adapt to a changing environment (Castren, 2010).

The findings that neurogenesis and neuroplasticity are involved in antidepressant response has led to the suggestion of a network hypothesis of depression. This hypothesis suggests that antidepressants reinstate a juvenile-like plastic state in which a depressed individual is able to alter networks in response to external signals. While increased monoamine levels are essential to antidepressants effects, increased neurotransmitter levels may not directly improve mood. Instead, they increase plasticity in dysfunctional limbic and cortical networks that allows an individual to adapt and change (Castren, 2013). One notable study in support of this theory showed that fluoxetine was able to generate increased neuroplasticity in rats. When young rats are deprived input to one of their eyes by suturing that eye shut during a critical period of development, they become blind in that eye, or amblyopic, even when they are allowed to use that eye after the critical period has ended. This blindness occurs because the visual cortex that would ordinarily receive stimuli from that eye does not develop if it is deprived of stimulus during the critical period. However, when these rats were treated with fluoxetine, and use of the bad eye was encouraged, their blindness was reversed. This reversal of blindness was associated with the reduction of GABA-ergic inhibition and increase in BDNF expression in the visual cortex. Interestingly, fluoxetine was only able to induce these changes when the amblyopic eye was used and the normal eye was not (Vetencourt et al., 2008). Similarly, environmental enrichment defined as increased exploratory behavior and sensory-motor stimulation

reverses amblyopia in rats by a similar mechanism involving reduced GABA-ergic inhibition and increased plasticity in the visual cortex (Sale et al., 2007). These findings suggest that rather than improving mood directly, fluoxetine and other antidepressants may provide the *potential* for change. It is noteworthy that cognitive remediation (Fisher, et al., 2016), rTMS (Shang, et al., 2016), and ECT (Rocha, et al., 2016), all of which alleviate depression, increase neuroplasticity and lead to release of BDNF (citation). While depressed patients lack the normal ability to adapt through neuroplasticity, effective treatment may entail reinstating this plasticity. This conception implies that biological treatments with psychopharmacology may not be sufficient alone, and that psychotherapy and/or efforts on the part of the patient are necessary to induce change and clinical improvement (Castren, 2013).

INTERACTION BETWEEN STRESS, INFLAMMATION, AND NEUROGENESIS

There is a strong interaction between the stress response, inflammation, and neurogenesis in health. In a review of the neuroendocrine and immune regulation of energy in the inflammatory response, Straub et al. (2010) describe the essential interaction between inflammation, the HPA axis, and the sympathetic nervous system. Below is a summary of some of the points most relevant to this discussion. An active immune response utilizes roughly 25%-30% of the basal metabolic rate, representing a very significant energy demand. In order to conserve energy, inflammation causes sickness behavior including reduced muscular, gastrointestinal, and mating activity. In health, the circadian rhythm creates high levels of glucocorticoids during the day to fuel activity. Conversely, at night glucocorticoid levels are low, whereas high levels of growth hormone provides glucose to immune cells. Notably,

"sickness behavior" induces increased sleep which in turn fuels an upregulated immune system, as immune cells are fueled primarily during sleep. These behavioral changes occur in response to increased cytokine levels. "Spillover" of cytokines such as IL-6 in the context of a robust immune response activates the HPA axis and the sympathetic nervous system, leading to increases in glucocorticoids, epinephrine, and NE respectively. The activation of the HPA axis allocates energy from distant sources, such as glucose and ketones from the liver, amino acids from muscle, lipids from fat, and calcium from bones. Similarly, stimulation of β2 adrenergic receptors by epinephrine increases glycogenolysis, gluconeogenesis, and lipolysis. As inflammation represents a high metabolic demand, cytokines increase HPA axis activity and induce sickness behavior in order to reduce energy expenditure while mobilizing distant energy sources (Straub et al., 2010). Another possible mechanism through which inflammation could lead to depression lies in the relationship between inflammation and neuroplasticity, through mechanisms such as synaptic pruning. Recent research in the field of schizophrenia has shown that certain aspects of the complement cascade, specifically C4A, is located in synapses, dendrites, axons, and cell bodies (Sekar et al, 2016). This finding implies a possible explanation of the association of polymorphisms in certain immune genes and an increased risk for schizophrenia, as the immune system appears to be involved in the remodeling of synapses that takes place in adolescence and early adulthood, a process called synaptic pruning. It is possible that increased inflammation may play a role in depression in a similar fashion, through the reduction of dendritic complexity leading to reduced functional connectivity in affect processing circuits. The effect of inflammation on the integrity of neurocircuitry will be discussed in more detail below.

The interaction between inflammation and the stress response is bidirectional, with inflammation causing upregulation of the HPA axis, as above, and glucocorticoids and the sympathetic nervous system increasing inflammation as well. Though glucocorticoids are well-known for their anti-inflammatory properties in clinical practice, recent research has led to the growing appreciation that glucocorticoids can actually be pro-inflammatory as well. Glucocorticoids increase inflammation by permitting catecholamine activation of immune cells and by causing white blood cells to leave circulation and travel to tissues (Sorrells et al., 2009). In addition, glucocorticoids have been shown to prime cytokine release by macrophages. When given 12 or 24 hours prior to lipopolysaccharides (LPS) inoculation, corticosterone caused macrophages to release increased levels of TNF-α, IL-1, and IL-6. This increased immune response was associated with increased activity of nuclear factor-kappa B, a transcription factor for many cytokines (Smyth et al., 2004). The findings that glucocorticoids enhance epinephrine's ability to stimulate inflammation and increase the activity of nuclear factor-kappa B suggest that stress hormones *potentiate* a stronger immune response rather than increasing inflammation directly. It is adaptive for the stress response to prime the immune system as many sources of infection are traumatic and related to "fight-or-flight" situations. An injury that could introduce a pathogen will stimulate an increase in epinephrine and glucocorticoids which will in turn help the organism mount a robust immune response (Black, 2003).

In addition, inflammatory cytokines have been shown to reduce monoamine levels in depressed patients through increased metabolism of tryptophan, which is an essential precursor of serotonin. Tryptophan, an essential amino acid needed for synthesis of serotonin, is metabolized through the kynurenine pathway to kynurenin (KYN) via the enzyme indoleamine 2,3-dioxygenase (IDO). Cytokines such as IFN-α, IFN-γ, IL-1, TNF-α, and

PGE2 induce IDO activity, leading to increased tryptophan metabolism (Weiss et al., 1999). As tryptophan is needed by bacteria for survival, the inflammatory response triggers the metabolism of tryptophan in order to control infection (Carlin et al., 1989). However, as tryptophan is needed for serotonin synthesis, its metabolism by IDO leads to reduced levels of serotonin and depressive symptoms as well. These findings provide an important connection between inflammation and serotonin depletion, providing a possible mechanism linking inflammation with sickness behavior and depression (Muller and Schwarz, 2007).

Finally, cytokines and glucocorticoids have been shown to decrease monoamines and reduce neurogenesis. An important experimental model of depression is the chronic unpredictable stress (CUS) model. This model subjects rats to inescapable stressors, causing behavioral changes that parallel depressive symptoms in humans such as anhedonia, reduced motivation, and despair. One important finding is that CUS has been shown to decrease monoamine levels in rats (Ahmad et al., 2010). In turn, low levels of serotonin have been shown to reduce neurogenesis. The dorsal raphe, the primary site for serotonin synthesis, sends serotonergic projections to the hippocampus. Denervation of these projections was shown to cause a reduction of newly generated granule cells in the dentate gyrus of the hippocampus, while reinnervation by 5-HT fibers reversed these changes (Brezun and Daszuta, 2000). Similarly, stimulation of 5-HT1A receptors has been shown to increase granule cell proliferation in the subgranular layer and subventricular zone of the hippocampal dentate gyrus (Bansar et al., 2004). These findings indicate that there is an inherent connection between serotonergic neurotransmission and neuroplasticity in the hippocampus, in which the reduced neuroplasticity in depressed patients may be caused or exacerbated by reduced serotonin levels.

NEUROCIRCUITRY MODEL OF DEPRESSION

In addition to the biological mechanisms described above, neuroimaging studies of depressed patients have found changes in functional connectivity in the neural circuits involved in affect regulation. A neurological model of affect regulation involves a neuroanatomical apparatus comprised of lower limbic centers that are reciprocally interconnected with higher cortical regions, as shown in figure 1. While limbic areas such as the amygdala, hippocampus, basal ganglia, and nucleus accumbens mediate raw unprocessed emotion, areas of the prefrontal cortex (PFC), such as the subgenual, medial, and dorsolateral PFC, as well as the cingulate cortex, mediate cognitive processing of emotions and top-down inhibition of the limbic system (Mayberg, 2003). When strong emotion is generated in the limbic system, the cortex inhibits limbic activity and processes the emotion in a way that is tolerable. In this conception, depression is viewed as a disruption in neurocircuitry. Rather than focusing on one biological factor or lesion, researchers have described a "functional lesion," in which there is a perturbation in the affect regulation system and an associated attempt at compensation (Mayberg, 2003). Depression can be caused by bottom-up phenomena, in which chronic hyperactivity of brainstem and limbic centers overwhelms the cortex's capacity, or a top-down mechanism in which hypoactivity or hypoconnectivity in the cortex precludes the necessary inhibition of normal limbic activity (Mayberg, 2003).

Several neuroimaging studies have lent support to this theory, and while it is beyond the scope of this paper to adequately review these findings here, it is helpful at this point to briefly mention some pertinent findings. In line with the theory of a top-down mechanism of depression, neuroimaging studies have found reduced volume in the prefrontal cortex, especially

in the subgenual prefrontal cortex, as well as in the amygdala, basal ganglia, and hippocampus (Sheline, 2003). These volume losses may be due to chronic hypoercortisolemia induced by functional hyperactivity of the HPA axis, which leads to neurotoxicity (Sheline, 2003). In addition to reduced volume, studies of patients with depression have shown functional hypoactivity in the subgenual prefrontal cortex, which is interconnected with the basal ganglia, amygdala, lateral hypothalamus, and brainstem seretonergic, noradrenergic, and dopaminergic nuclei (Drevets, 1997). Other studies have found hyperactivity in the prefrontal cortex in some depressed patients. These seemingly contradictory findings have been conceptualized in line with the theory of top-down inhibition, in which hypoactivity in the PFC leads to depressive affect accompanied by apathy, psychomotor retardation, and reduced executive functioning, while hyperactivity in these areas leads to psychomotor agitation and rumination (Mayberg, 2003).

[Figure 1 about here]

DISCUSSION: A UNIFIED THEORY OF DEPRESSION

In thinking about a unified theory of MDD, an analogy to other conditions that present with depressed mood is helpful. Among the many conditions that present similarly to MDD, two are relevant to this discussion: grief and adjustment disorder. In both these conditions, patients may experience depressed mood and neurovegetative symptoms, and their presentation may be indistinguishable from that of a major depressive episode. The difference between MDD and

these conditions is that the latter usually remit when the acute stressor or grief reaction has passed. Grief and adjustment disorder occur when there is an inability to tolerate and process an acute stressor or loss. While there exists a spectrum of vulnerability and resilience to stress (Figure 1), it seems reasonable to assume that almost anybody could suffer depressive symptoms if placed under a sufficient level of stress. What is important in these disorders is that for a number of reasons the normal capacity to tolerate stress or loss is overwhelmed, leading to depressive symptoms. As is depicted in figure 2, there exists a spectrum of depressive disorders, in which there is a continuum from a normal grief reaction through psychotic depression, based on the level of stress and vulnerability of the individual.

[Figure 2 about here]

An analogy between these disorders and MDD, in which the ability to tolerate and process stress is overwhelmed, is helpful. In the former conditions, what is abnormal is the stress; in MDD what is abnormal is the emotion-processing machinery. As described above, neuroimaging studies have found functional abnormalities in the affect regulation neurocircuitry in depressed patients, involving altered connectivity between cortical regions such as the PFC and subcortical regions such as the amygdala and hippocampus. Combining the above notion of a spectrum of stress and resilience with the neurobiological model of affect regulation, we can suggest that depression results when the affect regulation system is not adequately able to process strongly negative or depressive affect. This state is experienced by the individual as totally overwhelming and can lead to hopelessness and despair. While the common endpoint in this model is a tipping point, beyond which affect regulation is overwhelmed, this endpoint can be reached through several different pathways. These include psychological pathology, primary

alterations in the neuroanatomical regions themselves, and pathological changes in connectivity between these areas.

A primary focus of this paper is the fact that all of the proposed biological pathophysiological mechanisms of depression, including inflammation, increased stress response, and reduced neuroplasticity, are reciprocally connected with each other and the neurochemical pathways including the monoamines, glutamate, and BDNF. All of these pathways can also lead to the alterations found in the neurocircuitry of the affect regulation system, due to direct damage or reduced neuroplasticity in white matter tracts, leading to the observed expression of the illness such as depressive ideation and affect, motoric symptoms, and neurovegetative symptoms. (Figure 3).

This neurological system is strongly influenced by the psychological makeup of the individual. When a stimulus is experienced, it is processed and assigned a valence according to its psychological significance. Stimuli that are deemed meaningful enough can then trigger strong emotional responses in subcortical areas such as the amygdala, which are then processed in areas such as the cingulate cortex and the medial prefrontal cortex. Every stimulus is assigned meaning and affective valence as it is processed through cognitive schema and psychological organizations that are described by the field of psychology and are represented in exquisitely complicated neural interconnections between numerous brain regions. For instance, a patient who has a cognitive schema that is organized according to a core belief of being inadequate or unlovable will process stimuli accordingly, triggering strongly negative emotional responses in the amygdala. Similarly, an individual with disturbances in object relations or who harbors excessive intrapsychic conflict may also experience many objectively neutral stimuli as subjectively painful and stressful. It is also significant that many stressors actually stem from

internal sources, due to intrapsychic conflicts, an internalized sense of guilt or pathological object relations, etc. While stressors in experiments with animals usually relate to deprivation or pain, the near-infinite complexity of human psychology adds an important dimension of meaning to what are called psychosocial stressors. Accordingly, the psychological makeup of an individual is absolutely integral to an understanding of what stimuli will trigger strongly negative emotions, as well as how these emotions are processed. For instance, negative emotions will be intolerable to somebody with poor distress tolerance due to cognitive distortions or impaired ego strength. In essence, these psychological mechanisms are really ways to organize processes that involve the interconnection between brain regions involving subcortical centers of affect and emotion and the cortical areas that process these emotions. These psychological theories explain the complex way in which these circuits work together to process affect, the concept of self and other, and to contextualize experience. These psychological descriptions describe higher-order brain functions that entail the complex collaboration of numerous neural circuits working in tandem.

Primary biological derangements can also impair emotional processing. It is important to recognize that a genetic predisposition to an excessive amygdalar response to stress, or a hyperactive HPA axis due to early life stress, may generate inappropriately strong affect that overwhelms an otherwise healthy psychological system. In an analogy to a computer, the biological substrate represents the hardware, while the psychological mechanisms represent the software (Kendler, 2005). A defective software, or psychological issues, can make even objectively mild experiences overwhelming. Defective hardware, in the form of a biological pathology, can overwhelm an otherwise healthy software or psychological makeup. It is worth stressing that psychological mechanisms are just as biological as the primary biological

mechanisms described. Psychopathology stems from the maladaptive interconnections between emotional and cognitive circuitry. The distinction between a primary biological mechanism or a psychological one lies in whether there is pathology is the pattern in which these systems are organized, observed as psychological pathology, or in the brain centers or interconnections themselves, as manifested in diseased tissue and cells. To return to the analogy of a computer, the question is whether the computer has a functional hardware that was programmed improperly, or whether the software itself is correct, but the circuit-board has rusted. More often than not, there is a mixture of these factors, which impact each other bidirectionally. The biological findings in depressed patients, including monoamine depletion, HPA axis hyperactivity, inflammation, impaired neurogenesis, and ischemic damage, are all examples of malfunctioning hardware, as these mechanisms may cause reduced neurogenesis or white matter damage, which can impair the brain's ability to physically transmit and process emotional stimuli. Even if the individual's psychological makeup and emotion regulatory centers are healthy, if the interconnections between these areas, consisting of white matter tracts, are damaged through inflammation, hypercortisolemia, or ischemic damage, the affect regulatory pathway may be unable to adequately process negative emotions.

The above discussion shows how all of the proposed theories of depression are really just different nodes in an interactive matrix. The psychological makeup of a person dictates how each stimulus will be interpreted and assigned an emotional valence. The stimulus then triggers subcortical brain regions, generating an emotional reaction that is then relayed to higher cortical processing regions. This relay of information must traverse the brain's rich interconnecting networks whose functional utility is dependent on the biological integrity of the tissue. Any significant biological abnormality could damage these information processing

highways, leaving strongly negative emotions inadequately processed. Finally, as the information reaches cognitive centers in the cortex, they must be interpreted and processed according to the individual's psychological structure. It is also important to note that this psychological processing occurs via near-infinite interconnections between numerous cortical and subcortical regions, and as such, the psychological organization itself is subject to primary biological insults as well.

This highly complex neurological apparatus allows most people to deal with everyday stress with relative ease and functionality. However, when an acute stressor overwhelms the system, an otherwise healthy individual may develop an adjustment disorder. An objective loss that overwhelms the system may lead to grief. In these cases, the nodal problem lies in the external stimulus. However, when the dysfunctional node of the matrix is in the biological information relay system itself, mild stress or even normal stimuli can totally overwhelm a crippled brain. In these cases the brain simply cannot process the information adequately. Similarly, a biological predisposition to an excessive emotional response to stress, either through genetic factors or HPA axis hyperactivity due to early life stressors, slides a patient along the spectrum, so to speak, causing even objectively mild stressors to overwhelm the patient in a way that much more severe stressors would do to a healthy patient.

It is also significant that nearly all of the proposed pathophysiological mechanisms of depression are integrally related and interconnected. Psychological stress causes HPA axis hyperactivity, increased sympathetic outflow, and inflammation, which in turn cause ischemic damage to white matter and reduced neurogenesis. Inflammation causes HPA hyperactivity, which in turn has a permissive effect on inflammatory processes, creating a vicious cycle. Inflammation, reduced neurogenesis, and monoamine depletion are all interrelated. All of these

biological mechanisms, as well as a hyperactive amygdalar response, can also cause secondary psychological issues as the patient creates maladaptive cognitive schema or object relations to deal with such strong negative emotions. Focusing on any one of these mechanisms as the main cause of depression is far too reductionistic. Rather, all of these mechanisms occupy a position at a node in a complex interactive matrix of pathophysiological factors. The functional alteration at any node in the system can lead to malfunction of the entire matrix, with the end product being a depressive syndrome. The integrally interactive nature of the system dictates that triggering any one of the nodes can ultimately activate the entire cascade. Disorder lies not at one or several nodes, but rather in the *interaction among* them.

[Figure 3 about here]

A unified theory of depression is useful for several reasons. First, such a conception shows that a dichotomy between psychology and biology as the mechanism behind depression is unfounded. The preceding discussion makes it difficult to imagine a depression that could be purely biological or psychological without significant overlap. Similarly, the notion of one biological factor as the main etiology of depression is also less likely. Even if the initial cause is one psychological or biological mechanism, once the interactive matrix is triggered most patients probably have multiple factors contributing to their depression at once. Second, the description of MDD as several discrete conditions may represent a failure to appreciate the illness in all its complexity due to an inappropriately narrow scope of focus. It may be more useful to view depression as a final common pathway for many causative factors, acting singly or in combination. Third, this model could explain why different patients have such varying responses to antidepressant therapy, as well as why targeting some of the biological mechanisms involved

has had limited success. Targeting the monoamine system alone with antidepressants without addressing the other nodes in the system may simply be inadequate in some patients with strong biological or psychological predispositions to depression. Finally, a unified theory of depression could dramatically shift the focus of future research. A reductionistic approach to finding the sole biological cause of depression can entirely miss the essence of the condition, which lies in the interconnection of the various factors. Future research into how the nodes in the matrix are connected could elucidate the complex interactions involved.

While attractive, a unified theory of depression as a syndrome is not proven. It could well be that there are several dimensions of what we call depression that may or may not be related. In fact, there are at least several possible ways to conceptualize this disorder. The hypothesis presented here, that the pathophysiological mechanisms of depressive disorders represent one unified matrix, is one possibility. Another possibility is that there are several different subsyndromes of depression. For instance, there are patients who only have anhedonia, and nothing else, while there are others who may only have motoric underactivity or depressive ideation. In this conception, each subsyndrome may consist of a grouping of pathophysiological mechanisms into discrete groups that have little or no overlap. Finally, each pathophysiological mechanism may represent a discrete disorder. Thus the pathophysiology of depression may represent one disorder comprised of an interactive matrix of mechanisms, a few disorders representing separate groups of pathophysiological mechanisms, or numerous discrete biological mechanisms.

The interactive nature of each biological mechanism involved in depression lends support to the hypothesis that the phenotypic expression of depression stems from an underlying interactive matrix of factors. It seems less likely, though definitely possibly, that each biological

mechanism exists as a separate disorder. It is certainly possible that there are several discrete subsyndromes of depression. At this point, our lack of understanding of each biological mechanism limits our ability to directly test these hypotheses. Studying each of these domains and their neurobiological correlates across translational (R-DoC) levels will help us understand each biological mechanism in its details, after which a study of how these mechanisms interact will be possible. Thus, one way in which these hypotheses could be tested would be to continue the R-DoC project, with the ultimate goal of grouping patients according to the underlying pathophysiology of their disorder, subsequently mapping out the relationship between pathophysiology and its phenotypic expression.

CURRENT STATE OF THE EVIDENCE AND FUTURE DIRECTIONS:

If so much is known about the various biological causes of depression and their interactions, why have therapeutic interventions on these factors been either ineffective or incompletely utilized? Why is it that despite our understanding of so many aspects of the neurobiology of depression, our antidepressant therapies target increasing levels of serotonin, NE, and dopamine, without addressing all of the other factors? The answer to these questions may be due to the fact that while research has increased our understanding of which biological factors are involved in depression and that they interact with each other, it remains very unclear exactly how they do so on a molecular level. Without an understanding of the molecular mechanisms involved, creating effective therapies is close to impossible.

Through what mechanism do cytokines activate the HPA axis, and how do glucocorticoids potentiate the immune system? How exactly do both stress and inflammation reduce monoamine levels? The induction of tryptophan metabolism by IDO is one proposed mechanism, but this process remains incompletely understood. Reduced serotonin levels have been shown to reduce neurogenesis, but the precise mechanism remains unknown. The precise way in which genetic factors, such as a polymorphism in the 5-HT transporter gene, cause increased amygdalar reactivity is not fully understood. Perhaps most importantly, the proposed mechanism of reduced neurogenesis or white matter ischemia causing reduced functional connectivity between the sub-cortical centers and the cortex is far from worked out in its detail. The staggering complexity of these neural circuits and their interaction make the equation of reduced functional connectivity with depression overly simplistic. Perhaps most importantly, it is not clear whether many of these biological factors cause depression, or whether they are actually biological consequences of the condition. Unfortunately, without understanding the precise mechanism in which all of these factors interact and cause depression, it will remain difficult or impossible to intervene on any of them effectively. A more precise understanding of how these factors interact on a molecular level would allow for the development of drugs that could interrupt various stages of the pathophysiological matrix, perhaps halting the process.

In addition, the heterogeneity of depression poses a significant problem. There are numerous patholphysiological mechanisms involved in depression, but different patients manifest different combinations of these mechanisms. Often, the easiest approach to a complicated puzzle is to analyze each piece of the puzzle, one at a time. The current RDoC pradigm approaches psychiatric illnesses by identifying domains that run across different diagnoses and then identifying the various factors involved on every level of detail, from genes

and molecules to neural circuits and behaviors. The weakness of this approach is that it reduces what could be a complicated network of factors into isolated mechanisms. If, as we suggest here, the various biological mechanisms involved in MDD represent different nodes in a complex interactive matrix, then focusing on the elaboration of each individual factor may miss the entire essence of the disorder. Despite an increasingly sophisticated understanding of each mechanism, if we do not learn how these factors interact in overarching patterns, we may not come closer to understanding the disorder in a way that will inform treatment. It is reasonable to continue along the path of elucidating each individual factor in more detail, for without understanding each mechanism in depth it will be impossible to understand how various mechanisms interact. However, we must not make the mistake of being too reductionistic, searching for understanding in the pieces of the puzzle without understanding how they work together.

Future research will need to focus on working out the specific molecular mechanisms for the various interactions between the different systems. Increased understanding of any of the factors would likely be beneficial; however, it may be helpful to highlight one specific area that may be the most fruitful. Among the strictly biological pathophysiological factors in depression, the common end pathway appears to be reduced neurogenesis leading to functional hypoconnectivity in higher cortical regions and hyperconnectivity in limbic areas, as described by the network hypothesis; yet the precise way in which these biological factors lead to reduced neurogenesis or the way reduced neurogenesis leads to depression remains unclear. Targeting this common pathway with the goal of understanding how a hyperactive HPA axis, inflammation, and alterations in neurotransmitters cause reduced neurogenesis would be of paramount importance, as intervention at this level may hold great promise for good clinical outcomes. Since triggering any node of the matrix can lead to the stimulation of the entire

cascade, it seems reasonable to target a common end pathway, as intervening at this level could be effective regardless of the original etiological factors involved. Such developments may ensure that the wealth of knowledge acquired over the past few decades will be translated into new therapies and ultimately into better patient outcomes.

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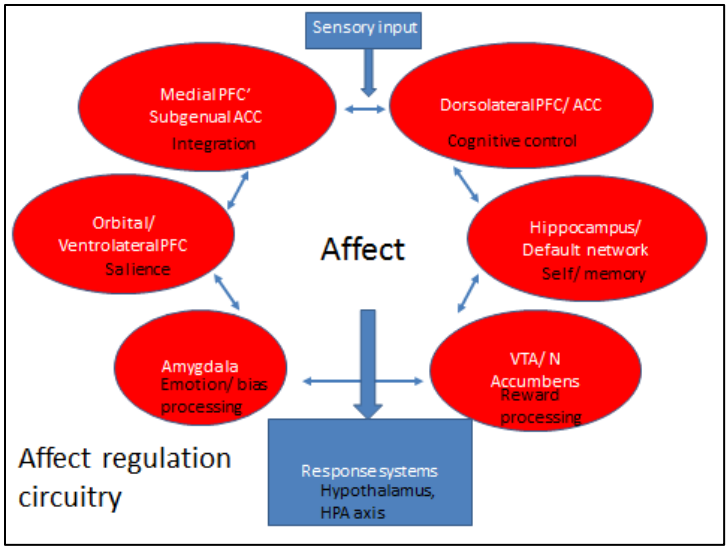

Figure 1. Affect regulation circuitry involving reciprocal connections between the cortex and subcortical regions.

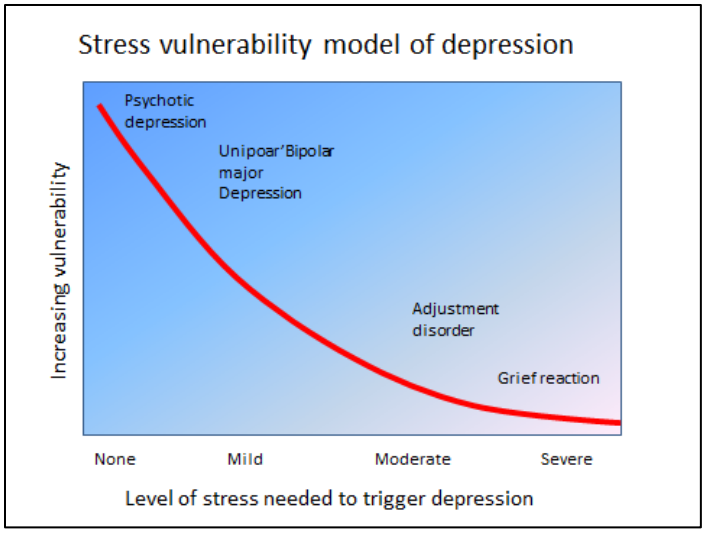

Figure 2. The stress-vulnerability model of depression. At increasing levels of biological vulnerability, even mild levels of stress can cause severe disorder.

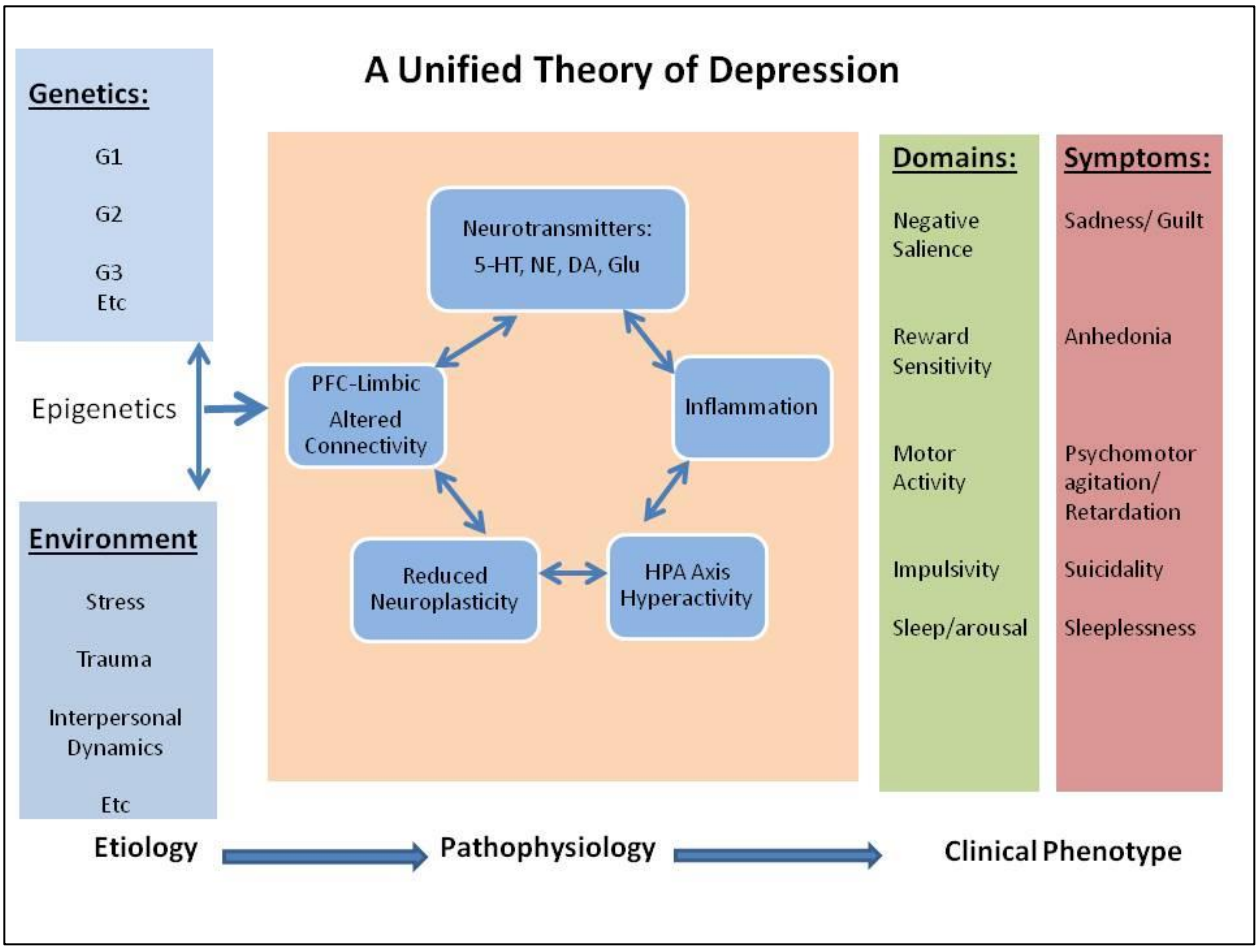

Figure 3. A unified theory of depression. Numerous genetic and environmental etiological factors interact to cause one or more reciprocally interactive pathophysiological mechanisms, which in turn cause symptomatic phenotypic expression in one or more R-DOC-like domains.