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VIEWPOINT

Depression: A malady of the self, arising from stress responses gone awry

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Major depression is one of the most significant disorders of our time. It is a heterogeneous, common, and complex disorder of gene–environment interactions, with multiple subtypes, including patients with melancholic or atypical features, that appear to stem from distinct clinical and physiological substrates. Stress is a disruptor of homeostasis and may pathologically extend into depression, particularly when adaptive responses become dysregulated. An integrated treatment approach, combining psychotherapy and pharmacotherapy, should target both the behavioral patterns and physiological underpinnings of depressive disorders.

Before describing how a stress response can evolve into clinical depression, I would first like to briefly discuss the scope of the problem and elucidate the clinical manifestations of depressive illnesses that can be construed as stress responses run awry.

Scope of the Problem

Clinically significant forms of depression affecting approximately 20% of individuals in the United States are likely to affect an equal number in populations around the world, depending on genetic characteristics and living conditions. The World Health Organization rates depression as the second most significant cause of disability worldwide and the greatest cause of disability in those under 45 years of age. While 60 million Americans have a major depressive illness, less than half are treated for depression with psychotherapy and pharmacotherapy, while the majority receive no treatment at all. In addition to causing great psychological anguish, disruption of families and interpersonal relationships, and the course of one's career (1, 2), the physiological manifestation of depression results in significant increases in the rate of premature systemic illnesses (3), such as premature coronary disease (4, 5), stroke (6), diabetes (7, 8), and osteoporosis (9), and shortens the lifespan by as much as ten years (10).

Clinical Manifestations of Different forms of Depression Subtypes

One of the key presentations of major depressive disorder (MDD) is depression with melancholic features, a DSM-5 specifier of depressive disorders, which constitutes roughly 30% of patients who develop MDD (11). Melancholic depression often contradicts the term depression in that it is often a state of increased vigilance and anxiety, especially about the value of the self. Indeed, melancholic depression intrudes upon many of the components that define our humanity (10). It is associated with a negative; one could even say malignant transformation characterized by the anguish of feeling thoroughly worthless (12, 13). A second malignant transformation is the loss of the capacity to anticipate or experience pleasure and even to remember past moments in life that brought pleasure and gratification. It is as if one had led a life saturated by despair and self-hatred, during which nothing of value was accomplished and most important interpersonal relationships failed. Many individuals with melancholic depression feel that life has no meaning. Hence, melancholic depression contributes significantly to those who feel the existential distress of living a meaningless existence in a meaningless world. For these reasons, I refer to melancholic depression as a profound disorder of the self (13, 14).

Melancholic depression is associated with a variety of physiological disturbances that produce premature systemic illnesses and shorten lives by as much as ten years. In particular, they experience the premature onset of coronary artery disease, stroke, diabetes, and osteoporosis. Physiologically, they have activation of the hypothalamic–pituitary–adrenal axis, the sympathetic nervous system, significant central nervous system and peripheral inflammation, increased hemoconcentration and coagulation, and activation of the renin–angiotensin system (14, 15).

A second phenotype of major depression seems, in many ways, the antithesis of melancholic or typical depression. It is called in the DSM-5 Major Depressive Disorder with atypical features in the DSM-5, and it is commonly referred to as atypical depression (10, 11). It is often associated with feeling out of touch with self and significant others, including spouses and children, feelings of emptiness, increased appetite, increased sleep, daytime fatigue and listlessness, and a significant incapacity to experience pleasure, anticipate a positive future, and consequent intense dysphoria. Patients with atypical depression have decreased levels of hypothalamic corticotropin-releasing hormone (CRH), plasma cortisol (16), increased plasma glucose, and increased inflammation (17), in part due to the weight gain occasioned by their increased appetite. In contrast to patients with melancholic depression, individuals with atypical depression feel worse in the evening than in the morning, when the stress response is relatively quiescent.

Rene Spitz made observations about infants and very young children who lived in orphanages. Although they initially responded to being left alone or hungry, as time progressed, they stopped showing overt emotional responses to deprivation. They seemed to lose interest in others and their environment. It was as if they had shut down their perceptual and emotional faculties to avoid the great distress of their impoverished state (18). Nonhuman primates separated from their mothers at birth and raised by those who were not much older than themselves showed emotional withdrawal and had very low cortisol levels (19). This presentation may share features of an extreme variation of atypical depression.

What is Stress?

Hippocrates wrote that we are all subject to disturbing forces that upset our equilibrium (20). We survive these disturbing forces because there are restorative forces that can re-establish homeostatic equilibrium. He called these restorative forces *Vis Medicatrix Naturae*, the healing power of nature (21). We now call the disturbing forces stressors, the balance homeostasis, and the healing forces adaptive responses (22).

Stress is a state of threatened homeostasis. Threats to homeostasis represent stressors that must be resolved to sustain homeostasis and viability. Uncontrollable stressors that threaten survival and are noxious promote the most profound stress responses. Stressors are almost always associated with increased vigilance and anxiety that represent calls to action, which often reflect conscious and unconscious sources. The stress

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response aims to promote survival and effective homeostatic set points. Thus, the stress response is one of our critical adaptative responses (23). Other adaptive responses include the immune response, which is responsible for providing effective answers to injury and infection. Like the stress response, the immune response can also run awry, manifested as autoimmune phenomena, characterized by immune responses to our own tissues and organs. Chronic stress decreases lifespan by many of its actions. In depression, a maladaptive stress response disturbs neuronal functions such as mood, cognition, and behavior, as well as multiple physiological responses throughout the body, which can predispose to premature systemic illness and shorten lives.

What Constitutes a Healthy Stress Response?

I chose an example of hikers in the woods who were notified that there was a forest fire nearby, which could threaten their survival. Their principal behavioral responses are hypervigilance, anxiety, and doing whatever they can to escape the nearby threat. It is essential that the hikers remain focused on the threat and are not distracted. One of the key means of ensuring that distraction does not occur is a substantial decrease in their propensity to be tempted by pleasant stimuli such as a beautiful site, food, sex, sleep, or other sources of gratification.

These adaptations are associated with significant changes in cognitive functions. There is a pronounced shift away from complex, sequence-dependent processes, and they focus exclusively on avoiding the dangers of the fire and getting back to safety.

Multiple physiological processes are also set into motion to prime metabolic, inflammatory, and coagulation processes. Blood glucose rises to assist the stressed brain. There is premonitory inflammation before injury occurs, so prepare for this contingency in advance. Blood clotting increases to prevent the sequalae of a possible hemorrhage occurring in a dangerous situation—their blood pressure, pulse rate, and cardiac contractility increase. The renin–angiotensin system is also premonitorily activated to protect from precipitous drops in blood pressure that might occur during dangerous situations. Unfortunately, these changes also occur reflexively in the context of psychological stressors such as test taking and defending one's ideas in classroom or work situations.

The question arises regarding why disturbances such as insulin resistance, increased plasma glucose levels, inflammation, and activation of the renin–angiotensin system occur as components of a normal response to physical or emotional stressors. In our early evolutionary history, the key stressors were conflicts regarding competition for mates, protecting the young, being hunted, and facing starvation. In these contexts, perceiving the possibility of danger meant that premonitory physiological changes adaptively occurred to prepare for possible injuries incurred during life-threatening circumstances. These early adaptations that have persevered into the present make significant contributions to the morbidity and premature mortality that occur in the of frequent or sustained psychological or physical stress (22).

Fortunately, when the hikers reach a safe place insulated from the dangers of a forest fire, their stress responses fundamentally resolve. They can think more clearly and in complex terms, enjoy everyday pleasures, their blood glucose levels return to normal, and resolve their inflammatory and coagulation processes. If these stress responses do not resolve but evolve into exaggerated and maladaptive behavioral and physiological states, depression can emerge, especially in genetically susceptible individuals.

The Interface between the Stress Response and Major Depression

During stress, anxiety and alarm are sufficient to promote effective action to cope with the danger and minimize harm, and thus, do not interfere with the capacity to maximize the likelihood of effective coping and survival (23). In MDD with melancholic features, fear, anxiety, and alarm are markedly more intense than during a normal stress response, producing hopelessness and anxiety that interfere with the capacity to take steps to overcome the depression. Thus, the symptoms of melancholic depression lock in the state, and depressive episodes can persist for long periods.

The stress response is associated with sufficient anxiety to promote substantial and practical efforts to avoid being hurt without interfering with adaptive functioning. In melancholic depression, fear, anxiety, and alarm can be profoundly greater than during stress, produce anguish and hopelessness, and interfere with the capacity to fight off depression.

In stress, cognition shifts from a propensity to tackle and deal effectively with complex situations and problems to instinctual or automatic actions that had previously worked in the context of manifest danger. In melancholia, concentration is impaired, and overall cognitive function diminishes. Moreover, cognition is often dominated by obsessive, ruminative preoccupations regarding fear, the deficiencies of the self, and the gloomy expected outcomes for such a defective self.

In a healthy stress response, there is a palpable decrease in the capacity to respond to pleasurable stimuli. This serves as protection against unwanted distractions. The decreased propensity to react to pleasant stimuli is insufficient to lead to demoralization that could interfere with an adequate stress response. In melancholia, the decrease in the capacity to anticipate or experience pleasure is pervasive and profound, leading to an incapacity to enjoy anything or remember ever being happy.

In response to stress, there is a tendency toward a decreased appetite and a decreased propensity to sleep, which allows total focus on the threat at hand. Stress does not usually lead to weight loss and loss of sleep and is ordinarily not nearly as severe as it is in melancholia. Melancholic patients lose their appetite, which can be life-threatening in the elderly, who also often have severe insomnia and marked early morning awakenings.

Activation of the CRH system, the sympathetic nervous system, and plasma glucose levels increase in a normal stress response to support the stressed body and brain. In addition, inflammation and coagulation are an inherent part of the normal stress response as the activation of stress hormone secretion to premonitorily anticipate and more effectively respond to injuries or hemorrhage occurring during a dangerous situation. The renin–angiotensin is also activated premonitorily. As mentioned, these changes occur to effectively anticipate loss of blood pressure due to hemorrhage or other factors during a stressful situation and promote survival. Stress–hemoconcentration is elevated in major depression and it is normalized by antidepressant treatment (15).

Melancholic depression is associated with a sustained elevation in the activity of the CRH system and the sympathetic nervous system, insulin resistance, increased plasma glucose levels, sustained inflammation in the brain and the periphery, and increased coagulation. Their sustained activation contributes to premature systemic diseases and premature deaths.

Taken together, the changes in melancholic depression indicate a stress system that has run awry, is excessively activated and is physiologically dysregulated.

We know less about atypical depression than we do about melancholia. We have shown, however, that patients with atypical depression have decreased activation of the CRH system and the pituitary–adrenal axis. In contrast to melancholia, their excessive sleep, daytime fatigue, and loss of a sense of connection to themselves and others suggest a stress system that is relatively inactivated.

Individuals with MDD and atypical features also manifest increased inflammation (17), noted earlier to reflect, in part, their weight gain secondary to their increased appetites. It is not known the extent to which distinct features of melancholic and atypical depression result in premature systemic illness and early death of patients with depression. While the physiological stigmata of melancholia are pretty likely to lead to these sequelae, it is unclear, except for inflammation, what might contribute to premature death in those with atypical depression.

The substantial data suggesting that MDDs reflect dysregulation of the stress response strongly support the validated premise that depressive illness responds best to a combination of psychotherapy and psychopharmacology. Stressful stimuli activate critical components of the stress system involved in the pathophysiology of affective illness and change its structure and function. Psychotherapy often helps in resolving maladaptive behaviors that promote interpersonal conflict and difficulties in work that, if they remain unchanged, can override the positive effects of psychopharmacology intervention.

An example of dysregulation of the stress system that seems relevant to the pathophysiology of melancholia is the loss of as much as 40% of

the volume of the subgenual prefrontal cortex in depression, particularly melancholia (24). The subgenual prefrontal cortex is involved in multiple components of the depressive syndrome. It estimates the likelihood of punishment or reward. It restrains the amygdala in its generation of fear. It primes the nucleus accumbens pleasure and reward center and restrains the CRH and sympathetic nervous systems. All of these are critical components of depressive illness.

The mechanisms by which a dysregulated stress response promotes and sustains depressive illness are currently being elucidated. We now know that major depressive illness is a neurodegenerative disease and that tissue is lost during the depressed phase not only in the subgenual prefrontal cortex but also in other prefrontal sites, such as the dorsolateral prefrontal cortex (10).

The role of stress in the pathophysiology of melancholia is better understood than in atypical depression. Stress produces excess cortisol and promotes CNS inflammation, which can be neurotoxic. Stress also downregulates the production and levels of brain-derived neurotrophic factor, whose deficiency is a crucial component of depressive illness and contributes to many of its stigmata, including not only lost neuroprotection and neuronal damage but decreased neurogenesis and neuroplasticity, also considered to be pathogenic factors in depressive illness.

Atypical depression occurs earlier in life than melancholia, is more often associated with childhood trauma, and tends to run a more chronic course. The downregulation of the stress response, which seems to occur in atypical depression, may produce behavioral withdrawal and suppression of overt emotionality as a defense against overwhelming pain. The downregulation of cortisol activity and attentiveness to external stimuli in nonhuman primates separated from their mothers at birth may provide a clue about the pathologic implications of a suppressed system. Low cortisol levels themselves can be associated with behavioral withdrawal and excessive fatigue. Future studies will likely uncover the behavioral and physiological consequences of a suppressed system and the mediators responsible for establishing and sustaining such a state.

I suggest that integrated treatment approaches, combining psychotherapy and pharmacotherapy, should target both the behavioral patterns and physiological underpinnings of depressive disorders and be tailored to address either decreased or increased stress responses according to MDD subtypes.

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