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# Stress, Depression can be related to Development of Parkinson's Disease

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## Abstract

This review aims to shed light on relationships involving childhood stress, depression. Stress early in life can contribute to the development of depression, and depressed patients are at risk of developing Parkinson's disease later in life. Depression commonly precedes the motor symptoms of Parkinson's disease. Stimulation of areas adjacent to the substantia nigra and dopamine (DA) agonists has been shown to reduce depression. Depression may therefore be part of the pathophysiological process leading to PD, rather than a simple mood disorder, as PD causes depletion of dopaminergic neurons in the substantia nigra. Mesocortical and mesolimbic dopaminergic pathways that mediate mood, emotion, and/or cognitive function may also play important roles in Parkinson's disease-related depression. Here, we propose that drugs designed to treat serotonin deficiency likely affect motor symptoms in depression-related PD.

**Keywords:** Stress; Depression; Parkinson's disease; Mood disorder

## Introduction

Stress is defined as sudden and inconsistent physical, physiological and social environmental changes experienced by an organism [1, 2, 3]. Exposure to stress in early childhood can have short-term or long-term effects on brain development, and these effects include learning disabilities and/or psychiatric disorders such as generalized anxiety and depression. [4, 5]. The mechanisms by which stress induces these psychological changes primarily involve the hypothalamic-pituitary-adrenal (HPA) axis [6, 7]. The HPA axis is a system that controls the organism's response to stress and modulates certain circadian activities [8, 9]. In response to stress, the HPA axis induces release of hormones (glucocorticoids and mineralocorticoids) from the hypothalamus, anterior pituitary, and adrenal cortex [8, 10]. For example, HPA axis activation stimulates the release of corticotropin releasing factor (CRF) from neurons in the paraventricular nucleus (PVN) of the hypothalamus, stimulating its release.of corticotropin releasing factor (CRF) from neurons in the paraventricular nucleus (PVN) of the hypothalamus which stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, which in turn, facilitates adrenal cortex to release cortisol/corticosterone [8, 10]. Additionally, the HPA axis has a negative feedback system that prevents excessive hormone secretion and sustained stimulation of these systems [11]. Studies have shown that corticosterone plays a role in suppressing prostaglandin synthesis, regulating immune responses, and negative feedback suppression on hormone release in the hypothalamus and anterior pituitary [8, 10, 12] . Early stressors, such as prenatal stress from the mother, early postnatal separation from the mother, early postnatal stress or early social isolation, can affect brain development and affect behavior over time. As such, it is associated with the development of psychiatric disorders [13, 14]. The immune response and exerts negative feedbacks inhibition on hormone release in the hypothalamus and the anterior pituitary gland [8, 10, 12]. Early stressors, such as prenatal stress from the mother, early postnatal separation from the mother, early postnatal stress or early social isolation, can affect brain development and affect behavior over time. As such, it is associated with the development of psychiatric disorders [13, 14]. Studies have shown that exposure to early maternal separation increases plasma ACTH and corticosterone levels in adult offspring, suggesting hyperactivation of the HPA axis [15, 16, 17, 18, 19]. Thus, high levels of corticosterone may result in blunted stress responses through desensitization of glucocorticoid (or mineralocorticoid) receptors at various levels of the HPA axis, preventing efficient negative feedback [18].

## Maternal separation

Early social interactions, including the bond between mother and offspring, are known to be important for social behavior and normal physiological development [20, 21]. Rodent-maternal isolation models have been used extensively to study the effects of early environmental exposure to stress on later life physiological and behavioral function [18, 22, 23, 24, 25, 26, 27]. This stress model is based on research showing that handling adult puppies for even short periods of time (10 minutes) each day can make them anxious [28]. Other studies have shown that removing pups from their mothers for 3 minutes each day reduces physiological responses to stress [29, 30]. Various maternal separation stress protocols (with varying duration and days of separation) have been used in laboratory animal studies to examine the short-term or long-term effects of stress on early childhood behavior. The duration of isolation can be considered short if it does not exceed 15 minutes and long if it lasts more than 3 hours [18, 27, 31]. Short-term maternal separation primarily assesses protective responses to stressors, whereas long-term separation may assess environmental factors that influence normal neurobiological development [32]. The duration and number of isolations (single or repeated) are important. Studies have shown that puppies separated from their mothers during the stress hyporesponsiveness period (2-14 days of age) have elevated levels of anxiety and/or depression [18, 33, 34, 35, 36]. The stress hyporesponsive phase is important in protecting the developing brain from high levels of glucocorticoids. High levels of glucocorticoids are associated with abnormalities in neurological and behavioral function, which can lead to neuropathological conditions such as depression [31, 34].

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## Depression and anxiety

Clinical depression, also called major depression or major depressive disorder (MDD), is a mental condition characterized by loss of pleasure or interest in almost any activity [37]. Based on symptom criteria, depression cannot be considered a single disorder, but rather a heterogeneous syndrome consisting of multiple symptoms with different etiology and pathophysiology [37]. Anxiety disorders are also psychiatric disorders with similar symptoms seen in depressed patients, but the difference is that anxiety may precede depression in most patients. The overlapping symptoms associated with depression and anxiety can complicate diagnosis, research, and treatment. Depression and anxiety are often referred to as stress-related disorders because they occur when people experience some form of chronic stress or emotional trauma in their lives [5]. Therefore, they can be perceived as major pathological changes that progressively affect brain structures via abnormal hormone secretion, ultimately affecting mental health [5]. Additionally, chronic stressful experiences usually lead to post-traumatic stress disorder (PTSD). This can be completely different from depression in terms of symptoms, treatment, and even the long-term course of the disease [37]. Because the mechanisms of stress leading to these psychiatric disorders are still poorly understood, we reviewed the literature to examine the neurobiology of stress leading to depression from a new perspective.

## Pathophysiology of stress leading to depression

There are many hypotheses that stress leads to depression, most of which involve altered levels of neurotransmitters such as dopamine, epinephrine, glutamate, gamma-aminobutyric acid (GABA), norepinephrine, and serotonin. Neurotransmitters are biochemicals that transmit signals between nerve cells in the brain and body. Most neurotransmitters can be both excitatory and inhibitory, depending on the receptors they activate. Dopamine is a neurotransmitter that modulates catecholamines and can be both inhibitory and excitatory [38]. Studies have shown that low dopamine levels are associated with Parkinson's disease. Noradrenaline/norepinephrine is also a catecholaminergic neurotransmitter involved in mood, motivation, emotion, and cognitive function. Serotonin is a monoamine neurotransmitter necessary to maintain a stable mood [39, 40]. Studies have linked serotonin deficiency to depression [39, 40]. Therefore, alterations in neurotransmitter release may correlate to some extent with the development of various psychiatric disorders, including depression. Because stress can disrupt the brain circuits or neural pathways that carry signals from these neurotransmitters, dysfunction of the HPA axis can lead to hormonal imbalances, behavioral disturbances, and/or mood disorders.

This may indicate an important role of the HPA axis in the development of neuropsychiatric disorders including depression. The current review focuses on his three hypotheses that suggest that stress disrupts neuronal processes and leads to depression which include:

## Noradrenaline hypothesis of depression

Norepinephrine is known to play a role in regulating emotions. Produced primarily in the locus coeruleus and affecting specific brain regions such as the prefrontal cortex, hippocampus and hypothalamus, norepinephrine/norepinephrine deficiency is associated with depression. Studies have shown that exposure to chronic stress, such as early separation from the mother, reduces levels of norepinephrine in the brain, leading to depression. It explains why selective norepinephrine reuptake inhibitors (SNRIs), a new class of antidepressants that act by increasing levels of depression [41].

## Serotonin (5-HT) hypothesis of depression

Serotonin (5-HT) is produced primarily in the dorsal raphe nucleus. Serotonin transporters take released serotonin from synaptic clefts into serotonergic neurons and help regulate various functions in the brain, including mood and emotion. The striatum, amygdala, and prefrontal cortex are, are regions of the brain innervated by serotonergic neurons. These brain regions, including the dorsal raphe nucleus, which is part of the brain's serotonergic system, are activated during early maternal stress. Abnormal levels of 5-HT in these brain regions are associated with depression. Preclinical and clinical studies have shown that childhood stress affects 5-HT levels in the brain, which can lead to depression [5]. Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressants commonly used to treat depression. SSRIs work by blocking 5-HT reuptake, thereby increasing the availability of 5-HT in the synaptic cleft and binding to receptors on the postsynaptic membrane. Therefore, by restoring levels of monoamines and their transporters in the brain, SSRI drugs are suitable treatments for dealing with early childhood stress disorders that lead to subsequent depression.

## Dopamine hypothesis of depression

Dopamine is produced withinside the substantia nigra pars compacta withinside the midbrain. Dopaminergic projections are known to be disrupted by stress in both the mesocortical and mesolimbic systems. Dopaminergic pathways are part of the reward system, and interactions between the dopaminergic system and the HPA axis, and between the dopaminergic and serotonergic systems, lead to chronic susceptibility to reward perception leading to depression. Stress effects can occur. Studies have shown that early psychological stress that activates the HPA axis exacerbates DA deficiency and is associated with decreased DA synthesis in the brain [5]. Offre et al. [42] and Leentjens [43] showed that administration of DA agonists can ameliorate symptoms of depression, highlighting the possibility that antidepressants have affinity for DA receptors. Since DA deficiency can be accompanied by depression, some antidepressants (SSRIs or SNRIs) may act on both the dopaminergic and serotoninergic systems to exert antidepressant effects. , DA deficiency resulting from childhood stress can in some cases predispose individuals to depression and ultimately to neurodegenerative diseases such as PD.

## Conclusion

Stress can trigger symptoms of neurodegenerative disease, revealing dysfunction that may have begun years ago. Treat the long preclinical phase with antidepressants such as fluvoxamine maleate; delaying the onset of neurodegenerative diseases may represent a novel approach and/or alternative method for extending life expectancy in individuals at risk of developing Parkinson's disease. Depressive symptoms are associated with dysfunction of her HPA axis, which plays an important role in the development of neurodegenerative diseases such as PD.

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