

How Neurotransmitters Shape Depression

Dhea Katkuri

Alliance Academy for Innovation, 1100 Lanier 400 Pkwy, Cumming, GA 30040, USA; dhearkatkuri@gmail.com

ABSTRACT: Depression has traditionally been explained as a chemical imbalance in the brain. However, growing evidence suggests that it involves interactions among neurotransmitters, brain networks, neuroplasticity, and environmental factors. Even though the chemical imbalance model has contributed to expanding knowledge concerning depression, this theory does not offer an explanation that can help account for the various reactions exhibited by different patients. More research is therefore needed to understand how neurotransmitters affect stress. This study analyzed the roles of serotonin, dopamine, norepinephrine, and glutamate in depression through a literature review of scientific journal articles. This review revealed that depression is understood as a disorder involving disruptions across interconnected brain systems rather than a deficiency of a single neurotransmitter. It has been determined that these neurotransmitters control the process of emotion, motivation, attention, the stress response mechanism, and neuroplasticity. Chronic stress triggers dysfunction of the hypothalamus-pituitary-adrenal axis, elevated concentrations of cortisol, reduced neurogenesis, and low BDNF levels. These findings suggest that depression develops through interactions among neurochemical, structural, and environmental influences. Understanding depression from an integrated systems perspective may support more personalized treatment approaches that combine medication, psychotherapy, and lifestyle interventions.

KEYWORDS: Cellular and Molecular Biology, Neurobiology, Depression, Neurotransmitters, Brain-derived Neurotrophic Factor (BDNF).

■ Introduction

For many decades, scientists have explored various areas of the brain in an effort to discover how different chemicals affect emotions and behavior. Serotonin is one of the most widely studied neurotransmitters that helps to regulate emotional responses. When serotonin signaling is impaired, people are more prone to experience depression and anxiety.^{1,2} Similarly, dopamine is an important neurotransmitter, responsible for regulating motivation, reward, and feelings of pleasure. Low levels of dopamine have been associated with anhedonia, which is the inability to feel pleasure, a symptom of depression.^{3,4} Another neurotransmitter, norepinephrine, is responsible for maintaining alertness and focus in a person and has been linked to fatigue and lack of concentration when not functioning properly.⁵ Moreover, glutamate is an essential neurotransmitter involved in the process of learning and memory formation in the brain. In recent studies involving ketamine administration, glutamate was also found to have mood-stabilizing and plasticity properties.^{6,7} All these neurotransmitters work together and influence emotion, motivation, attention, learning, and behavior at the same time.^{3,8}

With a better understanding of how the brain works, scientists have begun to question the idea that depression can be caused by a specific imbalance within the brain. Neurotransmitters, for example, do not work independently; rather, they affect each other and other systems in the body. Moncrieff *et al.* discovered that the data on the cause of depression is inconclusive since there was no scientific proof linking depression to the lack of serotonin levels in the brain.² Other research links problems in neurotransmitters such as dopamine and norepinephrine with symptoms including low energy, low mo-

tivation, and fatigue.^{3,9} Nevertheless, even though these studies clarify some characteristics of depression, they cannot account for the variety of symptoms experienced by patients. Therefore, researchers describe depression as a condition affected by neurotransmitters, stress hormones, neuroplasticity, and communication among different brain regions.^{3,8}

More recently, evidence for this broader perspective has been strengthened by large-scale brain networks, including the Default Mode Network (DMN). Studies have found that individuals with depression often show altered connectivity involved in self-reflection, emotional processing, and cognitive control.^{8,10} Increased activity within these networks has been linked to rumination, the repetitive negative thinking that commonly accompanies depression.⁸ These findings suggest that mental illness is influenced not only by the presence of specific neurotransmitters but also by how different brain regions communicate with one another. Neuroplasticity is an important part of this process because the brain's connections can strengthen, weaken, and reorganize in response to life experiences, environmental influences, and treatment.^{8,11}

Depression is also caused by chronic stress through the impact of stress on the hypothalamic pituitary adrenal (HPA) axis. Pariante and Lightman revealed that long-term stress can cause an impairment of the functioning of the HPA axis, increase cortisol secretion, and alter brain functioning.⁹ Sapolsky also noted that chronic exposure to glucocorticoids could be implicated in the shrinkage of the hippocampus and reduction in the number of neurons that could lead to the development of depression.¹² Another factor related to depression is Brain-Derived Neurotrophic factor. This protein, which stimulates neurons' growth and viability, has been implicated as a signif-

icant player in mood disorders. Depression could result from decreased BDNF activity, whereas successful therapy leads to increased BDNF activity.¹¹

This paper views depression not as a disorder caused by a single chemical imbalance, but as a condition involving multiple interacting brain systems. By examining neurotransmitter signaling, HPA-axis regulation, neuroplasticity, and brain network function, this paper explores the neurobiological mechanisms that contribute to depression. Looking at depression from this broader perspective helps explain why different people respond to different treatments. Medication, therapy, lifestyle changes, and stress management techniques may each target various parts of the same interconnected system. Research that demonstrates the effectiveness of antidepressants, psychotherapy, and emerging glutamatergic treatments further supports the need for a comprehensive strategy to treatment.^{6,7} Understanding these relationships may help researchers and clinicians develop more personalized and effective approaches to care.

■ Methods

This paper reviews the roles of serotonin, dopamine, norepinephrine, and glutamate in depression. Sources for this review were identified through searches of PubMed, Google Scholar, and library databases. Search terms that were used were “depression serotonin,” “depression HPA axis,” “depression BDNF,” “depression glutamate,” “depression reward system,” “major depressive disorder dysregulation of networks,” and “the involvement of dopamine in depression.”

This review is a narrative review rather than a systematic one because the goal was to synthesize the major findings across relevant studies, rather than to obtain every study that could be found using a meta-analysis. Sources were eliminated if they were not peer-reviewed, were mostly opinionated, were not related to depression, or did not directly speak to neurotransmitters, neural circuits, biology of stress, or depression.

A total of 18 primary sources including peer-reviewed journal articles, clinical trials and meta-analyses were reviewed based on their relevance, scientific significance, recency (2000–2026), and contribution to understanding the “chemical imbalance model” including perspectives that both challenged and expanded upon traditional neurotransmitter-based explanations, such as the review by Moncrieff *et al.*² In addition to neurotransmitter alterations, this review examined the roles of neuroplasticity, the HPA axis, and BDNF, all of which help mediate the effects of stress and the environment on the brain.^{9,11}

The DSM-5-TR definition of major depressive disorder was used to maintain diagnostic consistency in the reviewed literature.¹³ Most importantly, the study organized the results according to various functions served by these systems, such as affective regulation, motivation, and stress response, while noting the interactions among the systems, instead of isolating each from the other.^{4,5}

■ Results

Serotonin and Emotional Regulation Serotonin (5-HT) regulates the sensitivity, timing, and strength of neural responses to emotional stimuli.² It is not a fast-acting, localized generator of positive mood, but is more likely to modulate the strength, timing, and ordering of emotive responses. In this way, it may be thought of as a kind of global filter across the brain. 5-HT is produced from the amino acid tryptophan in the raphe nuclei of the brainstem, which project serotonergically to virtually every forebrain structure, including the prefrontal cortex, amygdala, hippocampus, and hypothalamus. The scope of its projection system allows wide-ranging influences on behavior and physiology, ranging from mood to impulse control to sleep.¹⁴ Following receptor activation, serotonin is taken up by the 5-HT transporter into the presynaptic neuron, and the availability of extracellular 5-HT is controlled by reuptake efficiency.^{2,14}

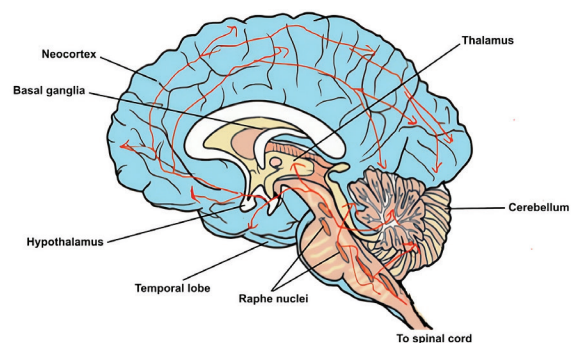


Figure 1: Simplified Serotonergic Pathways. Serotonin neurons originate primarily in the raphe nuclei and project throughout the brain, including the neocortex, thalamus, hypothalamus, and basal ganglia. The distribution of these pathways enables serotonin to influence mood, cognition, sleep, and other physiological functions. Redrawn from ref.¹⁸

As shown in Figure 1, serotonin pathways, which arise from the raphe nuclei, travel to different brain regions. Since serotonin pathways extend throughout the brain, it affects emotions, cognition, sleep, appetite, and physiological homeostasis.¹⁴ Different types of receptors are activated by serotonin, with the 5-HT_{1A} receptor, for instance, tending to reduce activity whilst calming the emotions, and the 5-HT_{2A} receptor increases activity in the cortex and has a central role in perception and cognition.¹⁴ This receptor heterogeneity enables serotonin to precisely modulate neural signaling in the brain without artificially boosting or reducing activity. So, reduction of their levels or receptor effectiveness will have reduced reliability in controlling the emotionally significant stimuli.^{5,14} It can be deduced that a reduction in serotonergic signaling might impair the brain's ability to regulate the emotional salience of stimuli, leading to a relatively higher attentional and memory-based salience of adverse events, consistent with the body of evidence for negative bias and emotional cognitive processing in depression.^{5,15}

For instance, a loosening of regulatory control may give rise to repetitive thoughts and worry, whereby small negative events are woven into a narrative that supports bigger (moral) failures. At the same time, a diminished restraint of the amygdala will intensify emotionality.^{4,8} Changes will also be

registered in eating and sleeping behaviors due to the implication of serotonin in circadian and hypothalamic processes.¹⁵ More serotonin in the brain does not necessarily equate with happiness; it may soon enhance the brain's capacity to more gradually maintain emotion and related behavior over time, and so return the affect regulation to a state such that the brain more readily manages that affectively salty moment without stressors generating stress.^{5,8}

With more reality-based amygdala activation and more powerful and effective PFC influences, a realm of optimal cognition and comportment, the neural states more gracefully hip up (prescribe a more context-appropriate state).^{8,14} An overabundance of serotonergic activity has the net effect of being effectively blunting or somnogenic.¹⁴ Its mission would seem to be to elevate and maintain one's default homeostatic state when one is not actually performing, as much as possible, to optimize positive functioning.

Similar to other neurotransmitter systems (dopamine, noradrenaline, and glutamate), Serotonin interacts extensively with them. Such interaction has profound influential effects on motivation, arousal, and plasticity and suggests a possible role of serotonergic activity in the middle of a control station responsible for the regulation of cognitive and affective processes.^{4,8} As a result, the extent to which serotonergic transmission is altered will influence perception, make sense of the environment, and respond to it. This further points to the pivotal role of serotonin and the neurobiology of depression.^{3,4,15}

Dopamine and Reward Dysfunction:

Dopamine itself is a monoamine and is part of the reward system in the brain, yet its main interpretation of its action is in regard to the regulation of motivation. It influences motivation as to how motivated an individual will be to attain a certain goal and how much effort they will put in (motivation).^{4,5} Dopamine is synthesized in the brain from a precursor amino acid, tyrosine, in cells by L-DOPA and is concentrated in neurons in the ventral tegmental area (VTA) and the substantia nigra.¹⁴

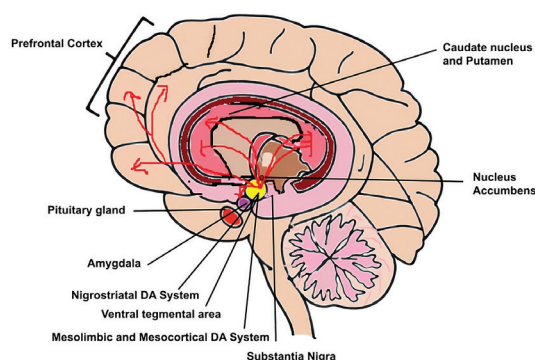


Figure 2: Simplified Dopaminergic Pathways. Dopaminergic neurons originate primarily in the ventral tegmental area and substantia nigra and project throughout the brain, including the nucleus accumbens, prefrontal cortex, amygdala, caudate nucleus, and putamen. These pathways enable dopamine to regulate reward processing, motivation, emotion, cognition, and motor function. Redrawn from ref.¹⁶

As shown in Figure 2, the dopaminergic pathways arising from these areas, indicated by the arrows, project to the pre-

frontal cortex and the nucleus accumbens, and this is where the pathways for reward and its behaviorally related stimuli originate.^{4,5,14} Dopaminergic fibers extending from these regions to the dorsal and ventral striatum constitute the mesolimbic and mesocortical pathways.^{4,8,14} These pathways are responsible for the reward-related responses, decision-making, and behavior.^{4,5}

Dopamine receptors within the synapses exist in two forms, the D1-like and D2-like receptors.¹⁴ These are mostly excitatory, enhancing current cell signaling, or inhibitory, and modulate feedback within the reward processing pathways. This enables dopamine to control the relationship between expectation and reward and outcome-reinforcing behaviors. In fact, dopamine is not simply a pleasure transmitter; it is implicated in reward prediction error signaling, sending a message when outcomes are either better or worse than anticipated, thereby helping to update behavior. A system like this is necessary for learning, habit formation, and the ongoing pursuit of useful activities.^{4,5,14}

In particular, a diminished dopamine mesolimbic transmission adversely affects the brain's capability to grant value to potential rewards. Reducing mesolimbic dopamine transmission may contribute to anhedonia, or a diminished ability to anticipate and experience reward.^{4,5}

In this state, the brain's ability to generate strong predictive reward signals is reduced. For example, a student understands that studying is a way to success, but he or she has no motivation coming from an anticipated reward to start studying. In the end, depression levels increase as the rewarding experiences become less and less frequent, leading to withdrawal and inactivity, which further worsens the state of depression.^{4,5}

In contrast, increases in dopamine can improve motivation, attention, and engagement in goal-related activities by making rewards feel more significant or worthwhile.^{4,5} This increases the likelihood that a person will start and continue a task because the connection between effort and positive outcome feels stronger. However, excessively high dopamine activity can also disrupt the brain's reward system and contribute to impulsive behavior, risk-taking, or addiction. This suggests that dopamine's role is not simply to increase pleasure, but to regulate motivation and reinforcement.^{4,14}

Dopamine also works closely with other neurotransmitters like serotonin, norepinephrine, and glutamate.^{4,8} Together, these systems regulate mood, manage alertness, and support cognitive flexibility. Because of this interaction, dopamine becomes part of the larger neural network involved in motivation and behavior. When these systems become dysregulated, depression can affect not only mood but also a person's ability to take action, pursue goals, and find meaning in daily life. This helps explain why dopamine is considered a key factor in the neurobiology of depression.

Norepinephrine and Stress Response:

Norepinephrine (noradrenaline/NE) is a monoamine neurotransmitter and hormone that governs waking stress, attention, and levels of arousal. For it to be able to govern different areas of the brain, NE must map out to different areas.

The neurotransmitter is synthesized from dopamine by the dopamine hydroxylase enzyme and is mainly produced by the locus coeruleus cells.

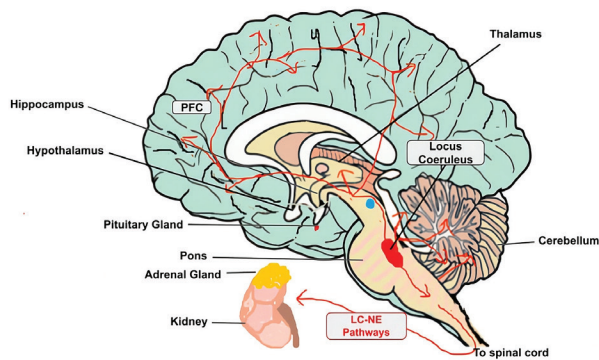


Figure 3: Simplified Locus Coeruleus Pathways. Noradrenergic neurons originating in the locus coeruleus project extensively throughout the brain, including the prefrontal cortex, hippocampus, hypothalamus, and thalamus, and interact with the HPA axis involved in the stress response. The widespread distribution of these pathways enables norepinephrine to regulate arousal, attention, cognition, and emotional processing. Redrawn from ref.¹⁷

As shown in Figure 3, the locus coeruleus cells have a wide and dense projection of the norepinephrine system throughout the brain. These give off axons to target different areas of the brain, including the prefrontal cortex, amygdala, hippocampus, and thalamus. This wide projection network is thought to enable the coordination of waking/cognition/emotion.

Norepinephrine acts at a synaptic level by way of adrenergic receptors, which are separated into alpha and beta types that influence neurons in various ways.¹⁴ Alpha-2 receptors tend to be inhibitory autoreceptors that stop norepinephrine release and restore normal function, whereas Alpha and Beta receptor types are typically excitatory. Through this receptor system, norepinephrine influences the brain's preparedness to react to stimuli, thereby regulating the degree of alertness and attention per the needs of the environment.

Unless the brain has enough norepinephrine, a person cannot stay awake and focused. Fatigue, slow thinking, and inability to concentrate are all symptoms that are caused by underactive brain cells that help us pay attention. This is sometimes called "mental fog", when even the simplest things seem exceedingly difficult. For instance, a student could find it extremely hard to do homework, not because he or she does not know the material, but because the brain cannot stay alert to the point that it could fully understand the material. Additionally, less norepinephrine means that the brain becomes less good at stress response, which results in less motivation and a lower level of reaction to external changes.^{5,14}

Norepinephrine increases arousal, alertness, and cognition when there is a need for quick reaction or sustained concentration. Moderate increases of Norepinephrine enhance concentration and goal-directed behavior in the prefrontal cortex. Excessive amounts of norepinephrine are indicative of hyperarousal due to chronic stress, which appears as anxiety, irritability, and "a superdominance" of threat-detecting systems. As the system becomes oversensitive to potential threats, environmental stimuli elicit exaggerated threat-detection signals, resulting in sleep dysfunction, "bad" decision-making,

and emotional lability. These six account for the comorbidity of depression and anxiety.^{5,9,14}

Comprehensive interactions exist between norepinephrine and the serotonin, dopamine, and glutamate systems, largely related to control of the hypothalamic, pituitary, and adrenal axis, which orchestrates the body's response to stress. Chronic activation causes increased cortisol levels, which alter norepinephrine activity, resulting in neuronal dysregulation. Norepinephrine acts as the major intermediary between physiological stress and cognition/emotion, raising the possibility that dysregulation causes not only a mood disturbance but a dampening of attention, pervasive fatigue, and physiological exhaustion.^{8,9}

Glutamate and Emerging Research:

Glutamate acts as the main excitatory neurotransmitter within the brain, facilitating rapid synaptic transmission and synaptic plasticity; in contrast to monoamine neurotransmitters, which were observed to subtly change the overall 'mood' of the brain, glutamate was observed to directly facilitate long-term potentiation or depression, and the formation or retraction of synapses. This is how the brain learns and forms memories. At the molecular level, glutamate has an effect on five receptor types. Most relevant in the CNS are N-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Such stimulation of glutamate receptors affects the opening of calcium channels and elicits diverse signaling pathways leading to changes in gene expression, synaptic growth, and long-term potentiation. Long-term potentiation is hypothesized to be the cellular explanation for learning through repeated strengthening of synaptic activity.¹⁴

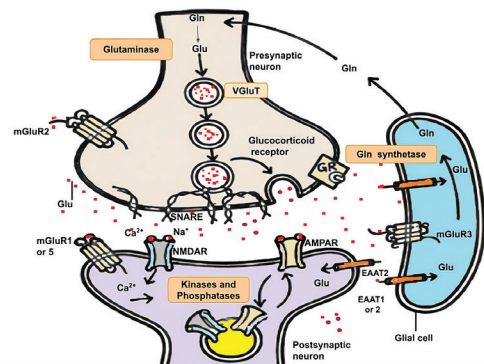


Figure 4: Simplified Glutamate-Glutamine Neurotransmitter Cycle. Glutamate released from the presynaptic neuron activates NMDA and AMPA receptors on the postsynaptic neuron, contributing to excitatory neurotransmission and synaptic plasticity. Excess glutamate is removed by astrocytic transporters and recycled through the glutamate-glutamine cycle, helping maintain neurotransmitter balance. Redrawn from ref.¹⁴

As shown in Figure 4, when glutamate signaling pathways become deregulated, plasticity decreases, compromising the connectivity between neural circuits, causing depression. Chronic stress also serves as one of the external factors that lead to depression, provoking an excessive release of glutamate in some brain regions, mainly in the prefrontal cortex. This excessive stimulation of calcium influx causes excitotoxicity, leading to neuronal damage, specifically characterized by den-

drift atrophy and a decrease in synaptic density. This leads to slower communication between areas involved in working memory and emotional regulation. The hippocampus, on the other hand, shows opposite responses, such as a decrease in glutamatergic activity and formation of synapses.^{7,11,14}

Depression causes physical damage to the brain tissue, which weakens the functional output. This is true within the hippocampus, where the brain's memory mediator and "reality sense" is to a larger extent than in several other parts of the brain, which explains the memory lapses often associated with depression; the brain is simply not capable of recording the experience, leaving the individual unable to remember anything new, the way in which it loses effectiveness and lacks alertness. With glutamate affecting what can only be called a blow to the brain's ability to affect itself, depression is a state of mental hibernation, immobile and depressed negativity.

Though central to bringing about peak functioning through reinstatements or replacements of glutamate, the transmission process takes hours. One example is the use of drugs like ketamine, an NMDA (N-methyl-D-aspartate) antagonist. By blocking NMDA receptor activity and triggering a cascade that enhances AMPAR transmission and neurotrophic factor expression, ketamine may promote synaptic plasticity, a mechanism that was proposed by Berman et al and Krystal et al to contribute to its rapid antidepressant effects.^{7,11} This fast and structural resolution of depression is not because its victims have had their own feelings directly ignored, but because their own cognition has been put into a functional state. It is this way that glutamate appears to be more than a facilitator over the poles of emotion: it is fundamental to the very mental mechanics through which individuals live in emotion. When glutamate regulation fails, depression becomes not just an emotion, but a structural breakdown of the brain.

Neuroplasticity and Brain Structure:

Though each neurotransmitter does necessarily have a different function, depression itself is a neuroplasticity disorder, a deficient adaptation in plasticity; the brain's ability to restructure itself.¹¹ Brain-derived neurotrophic factor (BDNF) is a key biological mediator of neuroplasticity and makes neuronal cell survival, growth, and synaptic communication easier.

Normally, through the action of BDNF, new neurons in the hippocampus are created in a process called neurogenesis. BDNF also aids in making synaptic connections stronger, which is a feature of learning and is also influenced by the environment. However, persistent stress and neurotransmitter imbalance for a long duration cause a drop in BDNF levels, and that diminishes the brain's ability to change and evolve.^{9,11}

This reduction is partly driven by sustained activation of the hypothalamic-pituitary-adrenal axis, which leads to repeated cortisol release. In addition to being the body's primary stress hormone, elevated cortisol can suppress BDNF production and contribute to structural changes in the brain. The hippocampus undergoes a slight reduction in size over time, while the connectivity and functioning of the prefrontal cortex are also impaired.^{8,10,12} These neuroanatomical changes do not merely correlate with the aging process but have functional

consequences.³ An under-sized hippocampus compromises context processing, which results in significant difficulty in differentiating between now and then, which threatens to continue negative effects by impairing the brain's ability to update its internal model of reality.^{8,12}

Similarly, when the prefrontal cortex becomes dysfunctional and cannot top-down control the brain's emotion reactivity hub, the amygdala, emotions will probably be less self-regulated and heightened. In fact, this would cause states of heightened emotion, in particular under duress or threat. Yet, affliction by 'depression' is not a cause for permanent change. Therapeutic intervention through treatment that brings neurotransmitter and diathesis parameters to 'normal' levels reduces the stress elicited and increases BDNF production and neurogenesis. Both neuroscience and psychological techniques have shown that these brain 'connectivities' can be enhanced, showing that the 'depressed' brain is capable of being transformed.^{10,11}

Integrated Systems Perspective: Network Dysregulation Rather Than Chemical Deficiency:

Modern neuroscience is moving away from the "one chemical" explanations for depression and is considering it a disorder of the whole brain, involving network dysfunction rather than one single neurotransmitter. Neurotransmitters do not operate in isolation, but are part of complex networks that govern cognition, emotion, and behavior. The problem is no longer one of "low" chemicals, but impaired messaging and interaction between brain regions. Another important set of pathways involves the interpretation of individual experiences.

Serotonin is involved with experience interpretation, dopamine with the perception of reward, norepinephrine with arousal and stress responses, and glutamate with neural plasticity.^{3-5,8} These pathways are constantly in a feedback loop with each other to either support good mental health or create a disturbed mentality.

An example of the effects of stress can be seen where the spikes in the level of cortisol dysregulate the function of norepinephrine and prompt an oversecretion of glutamate. Not only does this inhibit synaptic connectivity, but it also lowers BDNF levels, which impairs neuroplasticity, leading to a lack of control of emotion by serotonin and a lack of motivation by dopamine.^{9,11}

Given that depression is the result of the interaction of poor functioning of various systems, treatment must not only involve treating one neurotransmitter. For instance, traditional antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors may operate by gradually altering the signaling between serotonin and norepinephrine transmission. Certain drugs like ketamine and other recently discovered drugs in this class operate directly on Glutamate levels and establish a quick increase in nerve networks. Other SSRIs alone are inadequate, as the condition has an implication on conduct, thinking, and surroundings, too. Adjustments to the conduct and surroundings may prove particularly useful in reforming nerve cell function.

For example, apart from the increase in BDNF, regular physical activity also helps with neurogenesis and optimum

sleep-wake rhythms, maintains daily circadian rhythms, and supports neurotransmitters' circadian synchronization. On the other hand, cognitive behavioral psychotherapy brings intervention for training brain circuitry to function differently by interrupting negative thinking and reinforcing the prefrontal regions involved in emotion regulation.

These treatments do more than simply increase neurotransmitter levels. Over time, they help restore communication between neurons, allowing the brain to function more effectively. As these connections recover, the brain becomes better at adapting to challenges, processing emotions, and responding to the world around it.

This model accounts for observed differential symptom dimensions in depression across people. One person may experience only fatigue and anhedonia, another anxiety and hyperarousal, or another rumination and rigidity of cognition. These differential symptoms may prove to be certain dysfunctional nodes in a common network of neurotransmitters and neural systems. Overall, depression as a disorder of network disruption can elucidate the how and the why about the etiology and treatment of depression.

■ Discussion

Depression is not a single condition influenced by neurotransmitters or certain brain circuits, but it is a phenomenon resulting from neurophysiology and environment as well.^{9,11,15} To integrate information from various scientific fields such as neurobiology and medicine, this research attempts to study the role of serotonin, responsible for our emotions; dopamine, responsible for motivation and rewards; norepinephrine, influencing our ability to pay attention and cope with stress; and glutamate, involved in synaptic plasticity and adaptation.^{4,7,15} It should be added that neurotransmitters do not operate in isolation from each other but influence brain activities through forming feedback loops so that any dysregulation triggers changes in the activity of other brain circuits via processes such as chronic stress, HPA axis activation, and deficiency of BDNF.^{8,9,11} Thus, it can be said that the disorder of depression can be seen as one caused by dysfunction within the brain network, leading to emotional and mental changes that hinder actions, make people rigid, and unable to cope with stress.^{4,8}

This understanding of depression may also help guide treatment and prevention strategies. Because depression affects multiple interacting brain networks, treatment should be tailored to the individual. Monotherapy may not be sufficient for all patients. Combining conventional drugs, such as SSRIs, SNRIs, and ketamine, with behavioral interventions such as cognitive behavioral therapy (CBT), regular exercise, and adequate sleep may provide better outcomes by supporting neuroplasticity, improving emotional regulation, and reducing depressive symptoms.

■ Conclusion

Depression was once mainly understood as a biochemical dysfunction. However, research now suggests that it cannot be explained by the dysfunction of a single neurotransmitter

alone. When the communication between these brain circuits becomes disrupted, the brain struggles to manage stress, regulate emotions, and perform other normal cognitive functions. Serotonin, dopamine, norepinephrine, and glutamate do not work independently, but interact with one another through connected neural networks.

The adoption of such an understanding totally alters our conception of how we can treat the problem. The treatment for depression needs to go beyond the shortage of one chemical and incorporate several brain systems working simultaneously. Other interventions, such as clinical therapies, need to be supplemented by other approaches as well, such as healthy routines, socializing, and even a change in lifestyle. Depression is not just an emotional problem; it affects the brain's adaptation and response to change. Hence, the treatment should not focus on a single cause of depression but instead consider pharmacological, psychological, and behavioral factors that contribute to the disorder.

Future researchers should further investigate the mechanisms driving why individuals with depression often respond differently to the same treatment. Although many patients receive similar medications, some patients achieve full remission while others see no improvement. Examining genetic factors, environmental influences, and variations in brain network activity may help explain these disparities and support the development of more personalized approaches to treatment.

■ Acknowledgments

I would like to thank Professor Jobin Varkey for guiding me throughout this research project and helping me deepen my understanding of neurotransmitters and their impactful connection to depression. I also thank Professor Jen Tuban for reviewing and providing feedback that strengthened my work, and Coach Jo Kethar for keeping me motivated and providing me with these necessary resources. Finally, I owe my heartfelt thank you to my parents for giving me this opportunity to expand my knowledge on neuroscience as I continue to grow my interest and pursue medicine.

■ References

1. Caspi, A.; Sugden, K.; Moffitt, T. E.; Taylor, A.; Craig, I. W.; Harrington, H.; McClay, J.; Mill, J.; Martin, J.; Braithwaite, A.; Poulton, R. Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene. *Science* **2003**, *301* (5631), 386–389. DOI: 10.1126/science.1083968
2. Moncrieff, J.; Cooper, R. E.; Stockmann, T.; Amendola, S.; Hengartner, M. P.; Horowitz, M. A. The Serotonin Theory of Depression: A Systematic Umbrella Review of the Evidence. *Mol. Psychiatry* **2022**, *27*, 2397–2409.
3. Nestler, E. J.; Barrot, M.; DiLeone, R. J. Neurobiology of Depression. *Neuron* **2002**, *34* (1), 13–25. DOI: 10.1016/S0896-6273(02)00653-0
4. Russo, S. J.; Nestler, E. J. The Brain Reward Circuitry in Mood Disorders. *Nat. Rev. Neurosci.* **2013**, *14* (9), 609–625. DOI: 10.1038/nrn3381
5. Pizzagalli, D. A. Depression, Stress, and Anhedonia: Toward a Synthesis and Integrated Model. *Annu. Rev. Clin. Psychol.* **2014**, *10*, 393–423. DOI: 10.1146/annurev-clinpsy-050212-185606

6. Berman, R. M.; Cappiello, A.; Anand, A.; Oren, D. A.; Heninger, G. R.; Charney, D. S.; Krystal, J. H. Antidepressant Effects of Ketamine in Depressed Patients. *Biol. Psychiatry* **2000**, *47* (4), 351–354. DOI: 10.1016/S0006-3223(99)00230-9
7. Krystal, J. H.; Sanacora, G.; Duman, R. S. Rapid-Acting Glutamatergic Antidepressants: The Path to Ketamine and Beyond. *Biol. Psychiatry* **2013**, *73* (12), 1133–1141. DOI: 10.1016/j.biopsych.2013.03.026
8. Price, J. L.; Drevets, W. C. Neurocircuitry of Mood Disorders. *Neuropsychopharmacology* **2010**, *35* (1), 192–216. DOI: 10.1038/npp.2009.104
9. Pariante, C. M.; Lightman, S. L. The HPA Axis in Major Depression. *Trends Neurosci.* **2008**, *31* (9), 464–468. DOI: 10.1016/j.tins.2008.07.006
10. Schmaal, L.; Hibar, D. P.; Sämann, P. G.; Hall, G. B.; Baune, B. T.; Jahanshad, N.; Cheung, J. W.; van Erp, T. G. M.; Bos, D.; Ikram, M. A.; *et al.* Cortical Abnormalities in Adults and Adolescents with Major Depression. *Mol. Psychiatry* **2017**, *22* (6), 900–909. DOI: 10.1038/mp.2016.60
11. Duman, R. S.; Monteggia, L. M. A Neurotrophic Model for Stress-Related Mood Disorders. *Biol. Psychiatry* **2006**, *59* (12), 1116–1127.
12. Sapolsky, R. M. Glucocorticoids and Hippocampal Atrophy in Neuropsychiatric Disorders. *Arch. Gen. Psychiatry* **2000**, *57* (10), 925–935. DOI: 10.1001/archpsyc.57.10.925
13. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-5-TR*, 5th ed., text rev. American Psychiatric Publishing: Washington, DC, **2022**.
14. Stahl, S. M. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*, 4th ed.; Cambridge University Press: Cambridge, U.K., **2013**.
15. Belmaker, R. H.; Agam, G. Major Depressive Disorder. *N. Engl. J. Med.* **2008**, *358* (1), 55–68. DOI: 10.1056/NEJMra073096
16. Guy-Evans, O. Brain Reward System. *Simply Psychology*, **2026**. <https://www.simplypsychology.org/brain-reward-system.html> (accessed **2026-06-03**).
17. Driven Resilience. 3 Ways to Regulate Norepinephrine. **2018**. <https://home.hellodriven.com/articles/neurohack-your-brain-for-resilience-3-ways-to-regulate-norepinephrine> (accessed **2026-06-03**).
18. Shutterstock. *Serotonin System Diffuse Modulatory Systems Implicated*; Image ID 1621521616. <https://www.shutterstock.com/> (accessed **2026-06-03**).

■ Author

Dhea Katkuri is a student at Alliance Academy for Innovation in Cumming, Georgia, interested in pediatric medicine, neuroscience, and mental health. She believes that the early years of life are most pivotal because they influence long-term neurological development. Dhea plans to pursue an undergraduate degree in the biology track.