RESEARCH PAPER

Neurobiological Mechanisms of Depression and Anxiety Disorders: A Comprehensive Review of Current Evidence

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Abstract

Depression and anxiety disorders are among the leading causes of global disability, characterized by complex interactions between biological, psychological, and environmental factors. Increasing evidence suggests that their pathophysiology is rooted in intricate neurobiological mechanisms rather than isolated dysfunctions. This review aims to synthesise current evidence on the neurobiological mechanisms underlying depression and anxiety disorders, with a focus on neurotransmitter systems, neural circuitry, neuroendocrine regulation, neuroinflammation, and genetic influences. A comprehensive review of literature was conducted using databases such as DOAJ, Science Direct and Google Scholar. Relevant peer-reviewed articles were selected based on their focus on biological and neural mechanisms of depression and anxiety. The findings were organised into major thematic categories to facilitate systematic analysis. The review highlights that dysregulation of monoaminergic and glutamatergic systems, alterations in key brain regions such as the prefrontal cortex, amygdala, and hippocampus, and dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis play central roles in both disorders. Additionally, neuroinflammatory processes and genetic as well as epigenetic factors contribute significantly to disease vulnerability and progression. Substantial overlap in these mechanisms explains the high comorbidity between depression and anxiety. Depression and anxiety disorders are best understood through an integrative neurobiological framework. Advances in neuroscience and precision psychiatry hold promise for developing targeted and individualized treatment strategies.

Keywords: Depression, Anxiety disorders, Neurobiology, Neurotransmitters, HPA axis

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1. Introduction

One of the most widespread and crippling psychiatric disorders in the world, depression and anxiety disorders have a substantial impact on the emotional state of people, their cognitive abilities, and quality of life as a whole. These conditions are significant causes of the global burden of disease and the prevalence rates of such disorders are observed to rise among various people. Their extensive influence is not confined to the individual suffering, but also social functioning, productivity, and healthcare systems. Although the diagnosis and treatment of these conditions have improved, the multifactorial character of these conditions has remained a thorn in the flesh of clinicians and researchers alike.

The focus of the modern psychiatric research has been on the neurobiological processes that are involved in depression and anxiety. These disorders are no longer considered merely in terms of psychology or behavioural approaches but are becoming more defined as conditions, whose basis lies in complex biological processes, which include the brain, endocrine system, and molecular pathways. However, current studies emphasize that depression, specifically, is not related to one particular factor but a combination of various intertwining biological systems (Filatova et al., 2021). Equally, anxiety disorders are being more and more conceptualized as a disorder of neural circuitry, as a dysregulation of certain brain networks that process fear and regulate emotion (Gong, 2025).

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A number of theoretical constructs have been postulated to describe the biological nature of these disorders. One of the oldest and most widely used models is the monoamine hypothesis that indicates that the disproportion of neurotransmitters like serotonin, dopamine, and norepinephrine is key to the emergence of depressive and anxiety symptoms. Though this hypothesis has been used to inform pharmacological therapies over the past decades, current findings have shown it to be a partial explanation of the underlying pathology. The neuroplasticity hypothesis that highlights the importance of compromised synaptic plasticity and diminished neurogenesis in important brain areas, especially the hippocampus and the prefrontal cortex, has emerged as a result of neuroscience progress (Dean and Keshavan, 2017). This point of view emphasises the power of chronic stress and environmental effects to change the brain structure and functioning with time.

These theories are further supplemented by the stress-diathesis model, which combines the biological vulnerability with environmental factors. Under this model, the person is said to have a genetic or neurobiological predisposition, which can lead to depression or anxiety once subjected to some major stressors. The interplay between predisposition and the environment is justified by the increasing body of evidence in biomarker research, which indicates that biological indicators may be used to predict the vulnerability to depressive disorders (Kennis et al., 2020). These observations highlight the significance of both intrinsic and extrinsic factors in comprehending the development of diseases and their progress.

The high comorbidity rate is a characteristic of depression and anxiety disorders. Symptoms of the two conditions often occur in many people at the same time, implying common underlying mechanisms. Studies have shown that the presence of overlapping impairments in neural systems, neurotransmitter systems, and stress-response mechanisms contributes to this co-occurrence (Chen, 2022). This comorbidity makes it difficult to diagnose and treat since the conventional methods tend to treat these disorders as distinct entities, but not interconnected conditions. Variability in response to treatment also underscores the complexity of these disorders in addition to common biological pathways. There is a high percentage of patients who fail to respond well to the traditional therapies, and hence, the treatment-resistant depression is classified. This phenomenon has led to the reconsideration of the old models and the investigation of other processes, such as inflammation, neuroendocrine dysregulation, and genetic factors (Schroder et al., 2022). These insights have paved the way for more personalised approaches to treatment.

Recent progress in precision psychiatry seeks to overcome these problems with interventions designed to match an individual's biological profile. Researchers are striving to use genetic, neuroimaging, and molecular data to stratify patients based on their mechanisms and offer better therapeutic outcomes and a reduced trial-and-error approach to prescribing (Wang et al., 2026). This change is symptomatic of a larger trend of individualised medicine within mental health care. The neurotransmitter systems, especially the serotonin pathways, remain at the centre of the mood and anxiety disorders. Nevertheless, modern studies indicate that these systems are connected with more extensive neural systems and biological functions instead of acting on their own. As an example, the changes in serotonin signalling are currently interpreted within the framework of complicated brain systems that control emotion, cognition, and stress responses (McLaughlin, 2023). Such an integrative view is consistent with the recent attempts to abandon reductionist models in favour of a more detailed view of brain functioning.

Considering the complexity and interconnection of these processes, there is an increasing demand of integrative models that can integrate the understanding of various fields, such as neuroscience, genetics, and psychology, among others. These methods are necessary to capture the entire range of biological processes that occur in the depression and anxiety and to formulate more effective diagnostic and treatment interventions.

Thus, the current review will summarise the existing knowledge on neurobiological processes involved in depression and anxiety disorders. Through a combination of the recent research results, this paper aims at giving a detailed insight into the biological basis of these conditions especially focusing on neurotransmitter systems, neural circuitry, and new molecular pathways.

2. Methodology

This study uses a comprehensive review approach to explore key neurobiological mechanisms underlying depression and anxiety disorders. Relevant literature was collected from peer-reviewed journals, academic books, and credible scholarly sources, along with selected foundational studies to provide theoretical grounding. Searches were conducted through databases such as DOAJ, Science Direct, Web of Science, and Google Scholar using keywords including *depression neurobiology*, *anxiety disorders*, *neurotransmitters*, *brain circuits*, *HPA axis*, *neuroinflammation*, and *genetic factors*. Sources were selected based on their relevance to the biological, molecular, and neural mechanisms associated with depression and anxiety. The reviewed materials were then organised into major thematic categories, which guided the synthesis and discussion presented in this article.

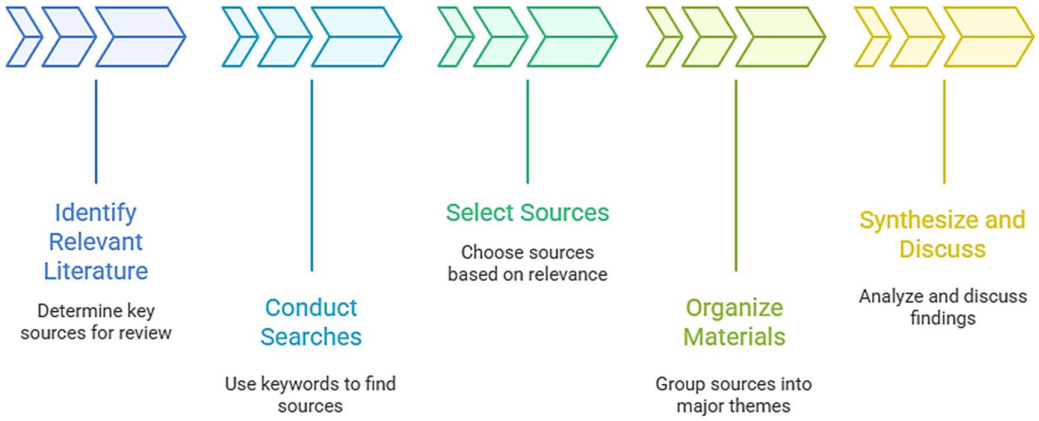

Figure 1. Overview of the Comprehensive Review Process

The complete review process used in this research is illustrated in Figure 1 below. These are the major stages involved in the review process: identifying literature on the topic; carrying out specific database searches; selecting sources that fit well within the framework of the paper; organising the literature according to different neurobiological concepts; and interpreting results from the literature reviewed. This methodology enabled a more integrative analysis of existing knowledge on the subject.

3. Results

3.1 Neurotransmitter Dysregulation in Depression and Anxiety

Imbalance of neurotransmitters continues to form one of the primary mechanisms behind both depression and anxiety disorders. Involvement of the monoaminergic system, including serotonin (5-HT), dopamine, and norepinephrine, in mood regulation, emotion processing, and responses to stress should be mentioned. Dysfunction of the serotonin neurotransmitter is closely related to depressive conditions, poor emotional regulation, and heightened anxiety state (Jauhar et al., 2023; Liu et al., 2018). Dopamine deficiency contributes to the development of anhedonia and reward-processing abnormalities, and dysfunction of the norepinephrine neurotransmitter causes disturbances in arousal. Apart from monoamines, the inhibitory and excitatory neurotransmitters, such as GABA and glutamate, are also critically important for the processes. The decrease of inhibitory effects of GABA combined with the increased influence of glutamate results in the change in neuronal excitability and emotional dysfunction (Duman et al., 2019; Lee et al., 2022). Table 1 contains information about the main neurotransmitters.

Table 1. Key Neurotransmitters and Their Functions

Neurotransmitter	Function	Role in Depression	Role in Anxiety	Supporting References
Serotonin (5-HT)	Mood regulation	Low levels, emotional instability	Increased fear and anxiety	Jauhar et al., 2023; Liu et al., 2018
Dopamine	Reward, motivation	Anhedonia, low motivation	Impaired reward processing	Li et al., 2021
Norepinephrine	Stress response	Fatigue, low alertness	Hyperarousal, panic	Liu et al., 2018
GABA	Inhibitory control	Reduced inhibition	Increased neural excitability	Duman et al., 2019
Glutamate	Excitatory signaling	Neurotoxicity, synaptic dysfunction	Heightened stress response	Lee et al., 2022

The above results show that the neurotransmitter system operates within a network, not independent of others. The role of interactions between neurotransmitters and the neural system, hormones, and the environment is what makes mood and anxiety disorders difficult to manage due to their complicated nature.

3.2 Neural Circuitry and Brain Regions

Neural circuit modifications within significant brain areas have been linked with both diseases. The PFC is crucial in regulating executive functioning and emotion regulation, while the amygdala controls emotions like fear. Modifications in these brain structures lead to poor emotional regulation and an increase in fear reactions (Robinson et al., 2019; Ressler, 2020). The hippocampus regulates memories and stress adaptation, and this brain region has been found to be defective in depression cases (Malhi & Mann, 2018). Additionally, dysfunction within large brain networks, such as the DMN, has been identified to cause ruminative and negative thoughts. Table 2 shows the primary brain areas and their malfunctioning.

Table 2. Brain Regions and Functional Roles

Brain Region	Function	Dysfunction in Depression	Dysfunction in Anxiety	Supporting References
PFC	Emotional regulation	Reduced control	Impaired fear regulation	Robinson et al., 2019
Amygdala	Fear processing	Negative bias	Hyperactivity	Ressler, 2020
Hippocampus	Memory, stress	Volume reduction	Stress sensitivity	Malhi & Mann, 2018
DMN	Self-referential thinking	Rumination	Excessive worry	Li et al., 2021
Amygdala–PFC Circuit	Emotion regulation	Disconnection	Fear dysregulation	Akiki et al., 2025; Gong, 2025

In general, interruptions within the neural pathways greatly influence the emergence and evolution of anxiety and depression. Lack of coordination between various areas in the brain that govern emotions and stress results in prolonged negative emotions, excessive fear, and poor cognitive function.

3.3 Neuroendocrine Mechanisms (HPA Axis)

The hypothalamus-pituitary-adrenal (HPA) axis represents a crucial element of the body's stress response. Imbalance of the HPA axis causes excessive production of cortisol, which adversely affects brain physiology (Gold, 2021; Menke, 2019). Prolonged exposure to stress causes hyperactivity of the HPA axis, disrupting feedback systems and making people more susceptible to mood and anxiety disorders (Akil & Nestler, 2023; Patriquin & Mathew, 2017). Table 3 summarizes important parts of the HPA axis, including changes in their physiology.

Table 3. HPA Axis Alterations in Depression and Anxiety

Component	Function	Alteration	Impact	Supporting References
Hypothalamus	Initiates stress response	Overactive	Chronic stress signaling	Patriquin & Mathew, 2017
Pituitary	Releases ACTH	Dysregulated	Prolonged stress response	Akil & Nestler, 2023
Adrenal Cortex	Produces cortisol	Elevated levels	Neurotoxicity	Gold, 2021
Feedback Mechanism	Stress regulation	Impaired	Sustained cortisol release	Menke, 2019
Chronic Stress	Adaptive response	Persistent activation	Mood disorders	Akil & Nestler, 2023

Such changes underscore the importance of the physiology involved in stress reactions for the development of psychiatric conditions. An imbalance within these systems will affect the hormones and the brain, leading to an increased risk for both depression and anxiety.

3.4 Neuroinflammation and Immune System Involvement

Increased levels of cytokines including IL-6 and TNF-α play an important role in depression and anxiety. The elevated cytokines affect neurotransmission and neuroplasticity (Felger, 2018). Also, activation of microglia increases synaptogenesis and leads to behavioral issues (Mehta et al., 2018). Table 4 highlights major aspects of inflammation and its impacts.

Table 4. Inflammatory Markers and Effects

Marker	Role	Effect in Depression	Effect in Anxiety	Supporting References
IL-6	Cytokine	Mood disruption	Stress sensitivity	Felger, 2018
TNF-α	Immune signaling	Neurotoxicity	Anxiety symptoms	Felger, 2018
Microglia	CNS immunity	Synaptic damage	Neural reactivity	Mehta et al., 2018
Neuroinflammation	Immune response	Fatigue, anhedonia	Fear amplification	Mehta et al., 2018
Chronic Inflammation	Persistent activation	Treatment resistance	Chronic anxiety	Felger, 2018

The results of such research support the recent theory on the involvement of the immune system abnormalities in the pathology of psychological problems. Changes in the functioning of the immune system can affect brain activity, neuromodulators, and neural connections, and consequently impact emotions and thinking. Therefore, it becomes clear that the importance of taking into account immune mechanisms cannot be overlooked.

3.5 Genetic and Epigenetic Factors

Genetic and epigenetic factors have a major influence on the risk of developing depression and anxiety disorders. Certain genes like serotonin transporter gene (SERT) and brain-derived neurotrophic factor (BDNF) are highly related to emotional regulation and stress (Kendler et al., 2022). Epigenetic mechanisms like DNA methylation control gene expression by altering the effect of stress from the environment and influencing behavior. The following table outlines some important genetic and epigenetic influences.

Table 5. Genetic and Epigenetic Factors

Factor	Role	Impact in Disorders	Supporting References
SERT Gene	Serotonin transport	Mood dysregulation	Kendler et al., 2022
BDNF	Neuroplasticity	Reduced resilience	Kamran et al., 2022
DNA Methylation	Gene regulation	Stress-related changes	Kuo et al., 2021
Gene–Environment Interaction	Combined influence	Increased vulnerability	Kendler et al., 2022
Epigenetic Changes	Adaptive regulation	Long-term effects	Kamran et al., 2022

The above-mentioned mechanisms indicate the tight relationship between the genetic susceptibility and the environment when it comes to mental disorders. Biological susceptibility raises the risk of developing a disorder, whereas environmental factors such as trauma or stress serve as triggers for changes at the neurobiological level that result in depression and anxiety.

3.6 Comorbidity and Shared Neurobiological Pathways

Both depression and anxiety often occur together, owing to similar neurological foundations. Similarities in dysfunction within neural pathways, especially between the amygdala and prefrontal areas, lead to similar manifestations, such as emotional regulation problems and increased stress response (Chavanne & Robinson, 2021). Similar disruptions in neurotransmitters and stress pathways, such as HPA axis malfunction and neuroinflammation, enhance this similarity (Tanaka & Chen, 2023; Rajkumar, 2022). Table 6 summarizes neurobiological similarities associated with comorbidity.

Table 6. Shared Neurobiological Pathways

Mechanism	Shared Role	Impact	Supporting References
Amygdala–PFC Circuit	Emotional regulation	Dysregulation	Chavanne & Robinson, 2021
Serotonin Dysfunction	Mood/anxiety	Common pathway	Tanaka & Chen, 2023
Glutamate Imbalance	Neural signaling	Instability	Duman et al., 2019
HPA Axis	Stress response	Chronic stress	Rajkumar, 2022
Neuroinflammation	Immune response	Symptom overlap	Felger, 2018

The findings demonstrate the reality that there is no definite difference between depression and anxiety; rather, the two disorders are associated with similar biological mechanisms.

4. Discussion

The results of this review underscore the fact that depression and anxiety disorders are a result of complex and interdependent neurobiological processes that include neurotransmitter dysregulation, neurotransmitter altered neural circuitry, stress-response systems, and molecular adaptations. These mechanisms do not act in isolation, but rather in a complex web, which affects emotional regulation, cognitive processing, and behavioral reactions. This integrative approach is in line with new theories that understand psychiatric disorders as a disturbance of the dynamics of brain systems instead of local dysfunctions (Naffaa, 2024).

One major theme that comes out of the findings is the essential nature of neural circuitry, especially of the amygdala, prefrontal cortex and hippocampus. The dysfunction of these circuits leads to the poor emotional regulation and increased threat perception. Neuroimaging results indicate that structural and functional abnormalities of these areas are consistently related to anxiety and depressive symptoms, which will support their significance in disease pathophysiology (Madonna et al., 2019). Moreover, the recent developments in the field of circuit-level analysis can give a better understanding of how maladaptive patterns of neural connectivity maintain pathological fear and emotional dysregulation (Akiki et al., 2025).

The combination of the findings with the current theoretical models provides a more detailed insight into these disorders. Conventional models, as the monoamine hypothesis, are still applicable but not sufficient on their own. Modern approaches to neurotransmitter systems focus on the interaction of neurotransmitter systems with larger neural networks and environmental influences. An example would be the neurochemical interaction of various signaling systems as one of the reasons behind the variability of symptoms and comorbidity, especially in disorders with chronic stress and pain (Ma et al., 2025). Likewise, the stress-diathesis model is attested by evidence that prolonged stress exposure can restructure brain morphology and brain functions, causing a person to become more susceptible to psychiatric disorders (Cardoner et al., 2024).

The other salient finding is that there is a significant overlap between depression and anxiety both on neurobiological and clinical levels. Functional imaging research indicates that all these disorders share similar activation patterns, indicating the existence of common underlying mechanism instead of disease entities (Chavanne & Robinson, 2021). Behavioral and developmental studies also suggest that early-life vulnerability and family factors may similarly cause both conditions to co-occur (Abel et al., 2024). These results highlight the significance of implementing transdiagnostic strategies, which consider common biological mechanisms.

Clinically, the findings have important implications. Pharmacological interventions based on the neurotransmitter systems, including selective serotonin reuptake inhibitors (SSRI) are still a pillar of treatment. Nevertheless, their unpredictably effective nature implies that more specific and personalized approaches to treatment are necessary. Research on biomarkers provides effective directions to enhance the selection of treatments and future results of the therapeutic response (Maron & Nutt, 2017). Simultaneously, progress in the knowledge of neural circuits has helped in the creation of new therapeutic strategies.

Newer therapies like ketamine-based therapies and neuromodulation methods (e.g., transcranial magnetic stimulation) are becoming a focus because of their capacity to induce a fast neural change and a synaptic change. The experimental research has shown that fear-related behaviors can be changed by targeted manipulation of a particular set of neural circuits, which offer a mechanistic foundation to new interventions (Baek et al., 2019). These methods represent a change in symptom-focused treatment to circuit-focused treatment approaches.

Along with biological interventions, there is an increased awareness of the significance of considering psychological and social aspects in treatment models. All-inclusive models that connect neural processes to behavioral and environmental conditions are becoming more popular in efforts to enhance mental health outcomes (Craske et al., 2023). This is an integrative approach that demonstrates the changing conceptualization of psychiatric disorders as complex issues in need of multidisciplinary solutions.

Although these developments have been made, a number of research limitations still exist. Neurobiological changes and clinical symptoms are only associated in a limited number of studies, which are based on cross-sectional design, making it impossible to draw a causal relationship. Also, the presence of heterogeneity in the groups of patients makes it difficult to interpret the results and to generalize them. Differences in diagnostic criteria and methodology also add to discrepancies between studies (Kehoe, 2017). Furthermore, neuroimaging and molecular techniques have progressed a great deal, but the challenge is how to translate them into clinical practice.

Among others, knowledge gaps that need more exploration are also found. Exact mechanisms in which treatment resistance especially in depression occurs have not been well established. Moreover, although there has been a great deal of work on finding neural and molecular correlates of these disorders, the interplay of various biological systems is still to be investigated. Indicatively, the interconnection of the immune system, neural circuits, and neurotransmitter systems is a topic of ongoing investigation. Behavioral research also indicates that perceptual and cognitive biases, including hypervigilance to threat, have underlying neural pathologies, but they are yet to be integrated into biological models (McTeague et al., 2018).

Lastly, the world effects of depression and anxiety highlight the need to further research on this area. The disorders are a significant health issue of the population, as they impact millions of people globally, causing a great deal of disability and economic loss (Santomauro et al., 2021). To tackle this challenge, more needs to be done to fill gaps between neuroscience, clinical practice, and strategies in the public health.

5. Conclusion

This review indicates that depression and anxiety disorders are multifactorial and complex disorders that are based on neurobiological mechanisms that are interconnected. There is evidence that changes in neurotransmitter systems, neural circuitry, neuroendocrine regulation and immune processes are all involved in the development and maintenance of these disorders. These conditions cannot be explained by only one theoretical framework but rather they can be explained using an integrative framework that considers the dynamic interaction between biological systems and environmental influences. The results also highlight the great overlap between depression and anxiety, especially regarding common neural mechanisms and stress reactions. This comorbidity highlights the importance of transdiagnostic practices in research and in clinical practices. There are encouraging prospects of making diagnosis and treatment more precise and effective using the new neuroimaging, molecular biology, and precision psychiatry. Although there has been some progress, some gaps still exist especially in comprehending resistance to treatment and how various biological systems interact. Future studies ought to be conducted on longitudinal and interdisciplinary studies to explicate these processes further. In general, a better comprehension of neurobiological mechanisms will be crucial to the creation of more effective, specific and individualized therapeutic interventions in depression and anxiety disorders.

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