

## Neurobiology of Stress and Its Role in Mental Health: Emerging Therapeutic Strategies

Asema Mahveen<sup>1\*</sup> Irfan bin Mustafa<sup>2</sup> Nazema Farheen<sup>3</sup>

<sup>1\*</sup>National Research Institute of Unani Medicine for Skin disorders, Hyderabad, Telangana

<sup>2</sup>Alive Health centre, Hyderabad, Telangana

<sup>3</sup>Government Nizamia Tibbi College, Hyderabad, Telangana

Date of Submission: 04-02-2026

Date of Acceptance: 14-02-2026

### Abstract

**Background:** Stress is a pervasive biological and psychological phenomenon that plays a central role in the development and progression of major mental health disorders. While acute stress responses are adaptive and essential for survival, chronic or dysregulated stress exerts profound neurobiological effects that contribute to psychiatric morbidity.

**Objective:** This review aims to synthesize current evidence on the neurobiological mechanisms underlying stress and to examine emerging therapeutic strategies targeting stress-related mental health conditions.

**Methods:** A narrative synthesis of contemporary literature was conducted, focusing on neuroendocrine, neurochemical, inflammatory, structural, and molecular alterations associated with stress, along with evolving pharmacological and non-pharmacological interventions.

**Results:** Stress activates the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic–adreno–medullary (SAM) system, leading to cortisol and catecholamine release. Chronic activation disrupts feedback regulation, promotes neuroinflammation, and alters neurotransmitter systems including serotonin, dopamine, norepinephrine, GABA, and glutamate. Sustained stress exposure induces structural and functional brain changes, particularly amygdala hyperactivation, hippocampal atrophy, and prefrontal cortex dysfunction, accompanied by reduced neuroplasticity and brain-derived neurotrophic factor (BDNF) expression. These alterations are implicated in depression, anxiety disorders, post-traumatic stress disorder, substance use disorders, and cognitive impairment. Emerging biomarkers such as cortisol profiles, inflammatory markers, neuroimaging correlates, and heart rate variability enhance stress assessment. Therapeutic advances include monoaminergic and glutamatergic agents, anti-inflammatory approaches, neuromodulation techniques, psychotherapeutic

interventions, lifestyle modifications, and integrative strategies.

**Conclusion:** Stress-related neurobiological dysregulation represents a critical pathway linking environmental adversity to mental illness. Integrative and personalized therapeutic models grounded in mechanistic insights are essential for improving prevention and treatment outcomes in stress-related psychiatric disorders.

**Keywords:** Mental Health, stress, anxiety, depression, Psychological

### I. Introduction:

According to the “World Mental Health Report” released by the World Health Organization (WHO) in 2022, 970 million people worldwide suffered from mental disorders, with 82% of them living in low- and middle-income countries. The prevalence rate in high-income countries is higher than that in low-income countries (1). In 2021, nearly 1 in every 7 people (1.1 billion) around the world were living with a mental disorder, with anxiety and depressive disorders the most common (2). While effective prevention and treatment options exist, most people with mental disorders do not have access to effective care. Many people also experience stigma, discrimination, and violations of human rights. A mental disorder is characterized by a clinically significant disturbance in an individual’s cognition, emotional regulation, or behaviour. It is usually associated with distress or impairment in important areas of functioning. There are many different types of mental disorders. Mental disorders may also be referred to as mental health conditions. The latter is a broader term covering mental disorders, psychosocial disabilities, and (other) mental states associated with significant distress, impairment in functioning, or risk of self-harm (3-7).

Promoting mental health and preventing mental health conditions is fundamental to the public mental health approach, but this area is under-researched and complex to change. In particular, the

extent to which the social determinants of mental health should be approached is often uncertain. Psychological stress is a major global burden of mental health disorders, including depression, anxiety, cognitive impairment, and post-traumatic stress disorder. Despite substantial advances in neuroscience, the precise neurobiological mechanisms linking stress exposure to the onset and progression of psychiatric conditions remain incompletely understood. Existing literature is often fragmented, focusing either on neuroendocrine pathways, inflammatory processes, or therapeutic interventions in isolation. A comprehensive synthesis integrating these dimensions is therefore warranted (8,9).

Recent developments in neuroimaging, molecular psychiatry, psychoneuroimmunology, and epigenetics have significantly expanded our understanding of how stress alters brain structure, function, and plasticity. Simultaneously, emerging therapeutic strategies ranging from neuromodulation techniques and anti-inflammatory agents to lifestyle and integrative interventions are reshaping stress management paradigms. However, a consolidated review that bridges mechanistic insights with evolving therapeutic approaches remains limited. This review aims to (i) critically examine the neurobiological mechanisms underlying stress responses, including HPA axis dysregulation, neurotransmitter alterations, neuroinflammation, and structural brain changes; (ii) explore the role of stress in the pathophysiology of major mental health disorders; and (iii) evaluate emerging pharmacological, neuromodulators, psychotherapeutic, and integrative strategies for stress-related mental health conditions. This review seeks to provide a translational framework that connects basic neurobiological findings with clinical applications, thereby supporting the development of more targeted and personalized interventions.

## II. Conceptual Framework of Stress

### 2.1 Historical Evolution of Stress Theory: Selye's General Adaptation Syndrome

The scientific conceptualization of stress began in the early 20th century, most notably through the work of Hans Selye, who introduced the term "stress" into biomedical discourse. Selye defined stress as the non-specific response of the body to any demand placed upon it and proposed the General Adaptation Syndrome (GAS) model to describe the physiological response to stressors. GAS consists of three sequential stages: the alarm reaction, resistance stage, and exhaustion stage.

During the alarm stage, the body activates the sympathetic-adreno-medullary (SAM) system and the hypothalamic-pituitary-adrenal (HPA) axis, leading to catecholamine release and cortisol secretion. The resistance stage is characterized by sustained physiological adaptation to ongoing stress, with continued glucocorticoid activity aimed at maintaining homeostasis. However, prolonged exposure results in the exhaustion stage, wherein adaptive capacity declines, increasing vulnerability to disease, including mental health disorders.

Although Selye's model was foundational, it was criticized for emphasizing physiological responses while underestimating psychological appraisal and individual variability. Subsequent theories incorporated cognitive and environmental dimensions of stress processing, expanding the understanding of stress beyond purely endocrine mechanisms (10,11).

### 2.2 Allostasis and Allostatic Load

To address limitations of static homeostasis models, the concept of allostasis was introduced by Sterling and Eyer and later expanded by McEwen. Allostasis refers to the process by which the body achieves stability through change, actively adjusting physiological systems to meet environmental demands. Unlike homeostasis, which implies constancy, allostasis emphasizes dynamic adaptation.

Repeated or chronic activation of stress-response systems—particularly the HPA axis and autonomic nervous system—leads to cumulative physiological burden known as allostatic load. Allostatic load reflects the "wear and tear" on biological systems due to repeated stress exposure and inefficient recovery. It manifests through dysregulation in cortisol rhythms, inflammatory cytokine elevation, metabolic disturbances, and structural brain changes, particularly in the hippocampus and prefrontal cortex. Elevated allostatic load has been strongly associated with depression, anxiety disorders, cardiovascular disease, and cognitive decline. Thus, this framework provides a mechanistic bridge linking chronic stress exposure to long-term mental and physical health outcomes (12,13).

### 2.3 Acute vs. Chronic Stress Models

Stress responses can be broadly categorized into acute and chronic forms, each with distinct neurobiological and clinical implications.

Acute stress is typically short-term and adaptive. It activates the SAM system and transiently stimulates glucocorticoid release, enhancing

alertness, memory consolidation, and survival-oriented behaviours. In controlled contexts, acute stress may improve cognitive performance and resilience.

In contrast, chronic stress involves prolonged or repeated exposure to stressors, resulting in sustained HPA axis activation, glucocorticoid receptor dysregulation, neuroinflammation, and impaired neuroplasticity. Chronic stress has been linked to hippocampal atrophy, amygdala hyperactivity, reduced brain-derived neurotrophic factor (BDNF), and heightened risk of mood and anxiety disorders. Animal models and longitudinal human studies consistently demonstrate that chronic stress produces maladaptive structural and functional brain alterations, underpinning its central role in stress-related psychopathology (14-16).

Distinguishing between adaptive acute responses and maladaptive chronic activation is crucial for understanding the transition from physiological stress responses to pathological mental health conditions.

### III. Neurobiology of Stress (17-27)

#### 3.1 Hypothalamic–Pituitary–Adrenal (HPA) Axis Dysregulation

Stress activates the HPA axis, leading to corticotropin-releasing hormone (CRH) secretion, adrenocorticotropic hormone (ACTH) release, and subsequent cortisol production. Cortisol normally follows a diurnal rhythm and exerts negative feedback at the hypothalamic and pituitary levels to maintain homeostasis. Chronic stress disrupts this feedback loop, resulting in sustained hypercortisolemia, glucocorticoid receptor resistance, impaired neuroplasticity, and increased vulnerability to mood disorders.

#### 3.2 Sympathetic–Adreno–Medullary (SAM) System Activation

Acute stress stimulates the SAM system, causing rapid catecholamine (epinephrine and norepinephrine) release. This enhances cardiovascular output and alertness. Persistent activation, however, produces autonomic imbalance characterized by sympathetic overactivity and reduced parasympathetic tone, contributing to anxiety, sleep disturbances, and cardiovascular risk.

#### 3.3 Neurotransmitter Alterations

Stress disrupts key neurotransmitter systems. Reduced serotonin levels are linked to depressive symptoms; altered dopamine signalling affects reward processing and motivation; norepinephrine dysregulation contributes to hyperarousal and vigilance. Imbalance between inhibitory GABA and excitatory glutamate transmission further impairs emotional regulation and cognitive function.

#### 3.4 Neuroinflammation and Cytokine Signalling

Chronic stress promotes the release of pro-inflammatory cytokines such as IL-6, TNF- $\alpha$ , and C-reactive protein (CRP). Microglial activation within the central nervous system amplifies neuroinflammatory responses. These findings support the inflammatory hypothesis of depression; wherein systemic inflammation contributes to mood dysregulation and altered neurocircuitry.

#### 3.5 Structural and Functional Brain Changes

Stress induces functional hyperactivation of the amygdala, enhancing fear and threat perception. Prolonged exposure is associated with hippocampal atrophy and impaired memory processing. Prefrontal cortex dysfunction compromises executive control and emotional regulation. Reduced brain-derived neurotrophic factor (BDNF) levels further impair neuroplasticity, reinforcing vulnerability to psychiatric disorders.

### IV. Stress and Major Mental Health Disorders

4.1 Depression: Chronic stress contributes to HPA axis dysregulation, neuroinflammation, and monoaminergic imbalance, central to the pathophysiology of major depressive disorder.

4.2 Anxiety Disorders: Heightened amygdala activity and sustained sympathetic arousal under stress increase susceptibility to generalized anxiety, panic, and related disorders.

4.3 Post-Traumatic Stress Disorder (PTSD): PTSD involves maladaptive stress responses, altered cortisol patterns, exaggerated fear conditioning, and impaired extinction learning.

4.4 Substance Use Disorders: Stress enhances dopaminergic reward pathway sensitivity, increasing risk for substance dependence and relapse.

4.5 Cognitive Impairment and Burnout: Persistent stress impairs hippocampal function, executive control, and attentional processes, contributing to cognitive decline and occupational burnout.

## V. Epigenetics and Gene–Environment Interactions

Stress influences gene expression through DNA methylation and histone modifications, altering neural plasticity and stress reactivity. Stress-induced epigenetic changes may persist long after exposure and, in some cases, demonstrate transgenerational transmission, underscoring the long-term biological imprint of adversity.

## VI. Emerging Biomarkers of Stress

Biomarkers include salivary and hair cortisol levels reflecting HPA activity; inflammatory markers such as IL-6 and CRP; neuroimaging correlates indicating structural and functional brain alterations; and heart rate variability (HRV), a non-invasive index of autonomic balance.

## VII. Emerging Therapeutic Strategies

### 7.1 Pharmacological Approaches

Pharmacological management of stress-related mental disorders primarily targets dysregulated neurochemical and inflammatory pathways. Selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) remain first-line treatments, modulating monoaminergic transmission and restoring synaptic serotonin and norepinephrine levels. Beyond monoamines, glutamatergic modulators such as ketamine and related agents target NMDA receptor pathways, offering rapid antidepressant effects and influencing synaptic plasticity.

Given increasing evidence linking chronic stress with neuroinflammation, anti-inflammatory strategies—including cytokine modulators and non-steroidal anti-inflammatory agents—are being explored as adjunctive therapies. Additionally, adaptogenic compounds, including plant-derived bioactives, are proposed to enhance stress resilience by stabilizing HPA axis activity and improving neuroendocrine balance. Together, these pharmacological advances reflect a shift toward mechanism-based interventions targeting stress-induced neurobiological alterations.

### 7.2 Neuromodulation Techniques

Neuromodulatory interventions aim to directly influence dysfunctional neural circuits implicated in stress-related disorders. Repetitive transcranial magnetic stimulation (rTMS) non-invasively modulates cortical excitability, particularly in the dorsolateral prefrontal cortex, improving mood regulation and cognitive control. Transcranial direct current stimulation (tDCS) delivers low-intensity electrical currents to alter neuronal membrane potentials and enhance cortical plasticity.

Vagus nerve stimulation (VNS), through modulation of autonomic and limbic pathways, has demonstrated potential in reducing depressive symptoms and regulating inflammatory responses. These techniques represent promising alternatives or adjuncts for treatment-resistant stress-related psychiatric conditions.

### 7.3 Psychotherapeutic Interventions

Psychotherapeutic approaches remain central to stress management. Cognitive Behavioural Therapy (CBT) addresses maladaptive cognitive patterns and promotes adaptive coping strategies, thereby modifying stress appraisal mechanisms. Mindfulness-Based Stress Reduction (MBSR) enhances present-moment awareness and reduces emotional reactivity, contributing to improved autonomic balance and decreased HPA axis hyperactivity.

Trauma-focused therapies, including exposure-based and cognitive processing approaches, are particularly effective in post-traumatic stress disorder, facilitating fear extinction and emotional integration. These interventions exert measurable neurobiological effects, including improved prefrontal regulation and reduced amygdala hyperactivity.

### 7.4 Lifestyle and Behavioural Interventions

Lifestyle modifications play a foundational role in stress mitigation. Regular physical exercise promotes neurogenesis and increases brain-derived neurotrophic factor (BDNF) expression, enhancing neuroplasticity and cognitive resilience. Adequate sleep is essential for restoring circadian cortisol rhythms and maintaining HPA axis stability.

Emerging evidence in nutritional psychiatry highlights the role of diet in modulating inflammation, gut-brain axis signalling, and neurotransmitter synthesis. Balanced dietary patterns rich in omega-3 fatty acids, antioxidants, and micronutrients may contribute to improved stress adaptation and emotional well-being.

### 7.5 Integrative and Complementary Approaches

Integrative strategies increasingly complement conventional therapies. Unani medicine and meditation practices regulate autonomic tone, reduce sympathetic overactivity, and improve emotional regulation. Herbal adaptogens and traditional medicine systems propose multi-target mechanisms, including modulation of stress hormones, antioxidant pathways, and inflammatory mediators.

## VIII. Translational Implications and Future Directions

Advances in precision psychiatry are reshaping stress-related mental health care by emphasizing individualized risk profiling and targeted intervention strategies. Personalized stress assessment integrating genetic susceptibility, biomarker panels, and psychosocial variables may enable tailored therapeutic approaches. Multi-omics platforms combining genomics, epigenomics, proteomics, and metabolomics hold promise for identifying novel biomarkers and mechanistic pathways linking stress to psychopathology. Furthermore, digital mental health technologies including wearable devices, mobile applications, and real-time physiological monitoring facilitate continuous stress tracking and early intervention. Future research should prioritize longitudinal, translational studies to bridge neurobiological insights with clinical practice, ultimately advancing personalized and integrative models of stress management.

## IX. Limitations of Current Evidence

Current evidence is limited by heterogeneity in stress measurement, cross-sectional designs, small sample sizes, and variability in biomarker standardization. Longitudinal and translational studies are needed to establish causality and therapeutic efficacy.

## X. Conclusion

Stress exerts profound neurobiological effects involving endocrine, inflammatory, and neuroplastic mechanisms. These alterations contribute significantly to the development of major mental health disorders. Integrative, personalized, and mechanism-based therapeutic models are essential for advancing effective stress management strategies.

### References:

- [1]. Freeman M. (2022). The World Mental Health Report: transforming mental health for all. *World psychiatry : official journal of the World Psychiatric Association (WPA)*, 21(3), 391–392. <https://doi.org/10.1002/wps.21018>
- [2]. 2021 Global Burden of Disease (GBD) [online database]. Seattle: Institute for Health Metrics and Evaluation; 2024 (<https://vizhub.healthdata.org/gbd-results/>, accessed 13 August 2025).
- [3]. World Health Organization. World mental health report. Transforming mental health for all. Geneva: World Health Organization, 2022. [Google Scholar]
- [4]. World Health Organization. Global action plan on the public health response to dementia 2017-2025. Geneva: World Health Organization, 2017. [Google Scholar]
- [5]. World Health Organization. Intersectoral global action plan on epilepsy and other neurological disorders 2022-2031. Geneva: World Health Organization, in press. [DOI] [PubMed]
- [6]. World Health Organization. Global strategy to reduce the harmful use of alcohol. Geneva: World Health Organization, 2010. [DOI] [PMC free article] [PubMed] [Google Scholar]
- [7]. World Health Organization. The world health report 2001. Mental health: new understanding, new hope. Geneva: World Health Organization, 2001.
- [8]. Kirkbride, J. B., Anglin, D. M., Colman, I., Dykxhoorn, J., Jones, P. B., Patalay, P., Pitman, A., Sonesson, E., Steare, T., Wright, T., & Griffiths, S. L. (2024). The social determinants of mental health and disorder: evidence, prevention and recommendations. *World psychiatry : official journal of the World Psychiatric Association (WPA)*, 23(1), 58–90. <https://doi.org/10.1002/wps.21160>

- [9]. Crielaard, L., Nicolaou, M., Sawyer, A., Quax, R., & Stronks, K. (2021). Understanding the impact of exposure to adverse socioeconomic conditions on chronic stress from a complexity science perspective. *BMC medicine*, 19(1), 242. <https://doi.org/10.1186/s12916-021-02106-1>.
- [10]. Selye H. (1951). The general-adaptation-syndrome and the diseases of adaptation. *Southern medicine and surgery*, 113(10), 315–323.
- [11]. Selye H. (1946). The general adaptation syndrome and the diseases of adaptation. *The Journal of clinical endocrinology and metabolism*, 6, 117–230. <https://doi.org/10.1210/jcem-6-2-117>
- [12]. Sterling P, Eyer J. Allostasis: A new paradigm to explain arousal pathology. In: Fisher S, Reason J, editors. *Handbook of Life Stress, Cognition and Health*. New York: Wiley; 1988. p. 629–649.
- [13]. Pshennikova M. G. (2000). Fenomen stressa. Emotsional'nyĭ stress i ego rol' v patologii [The stress phenomenon. Emotional stress and its role in pathology]. *Patologicheskaiia fiziologiia i eksperimental'naia terapiia*, (3),.
- [14]. Lupien, S. J., Maheu, F., Tu, M., Fiocco, A., & Schramek, T. E. (2007). The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain and cognition*, 65(3), 209–237. <https://doi.org/10.1016/j.bandc.2007.02.007>
- [15]. McEwen B. S. (1999). Stress and hippocampal plasticity. *Annual review of neuroscience*, 22, 105–122. <https://doi.org/10.1146/annurev.neuro.22.1.105>
- [16]. Arnsten A. F. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature reviews. Neuroscience*, 10(6), 410–422. <https://doi.org/10.1038/nrn2648>
- [17]. McEwen B. S. (1998). Protective and damaging effects of stress mediators. *The New England journal of medicine*, 338(3), 171–179. <https://doi.org/10.1056/NEJM199801153380307>
- [18]. McEwen B. S. (2007). Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiological reviews*, 87(3), 873–904. <https://doi.org/10.1152/physrev.00041.2006>
- [19]. Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature reviews. Neuroscience*, 10(6), 434–445. <https://doi.org/10.1038/nrn2639>
- [20]. Arnsten A. F. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature reviews. Neuroscience*, 10(6), 410–422. <https://doi.org/10.1038/nrn2648>
- [21]. Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature reviews. Neuroscience*, 9(1), 46–56. <https://doi.org/10.1038/nrn2297>
- [22]. Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biological psychiatry*, 65(9), 732–741. <https://doi.org/10.1016/j.biopsych.2008.11.029>
- [23]. Yehuda R. (2002). Post-traumatic stress disorder. *The New England journal of medicine*, 346(2), 108–114. <https://doi.org/10.1056/NEJMra012941>
- [24]. Kim, J. J., & Diamond, D. M. (2002). The stressed hippocampus, synaptic plasticity and lost memories. *Nature reviews. Neuroscience*, 3(6), 453–462. <https://doi.org/10.1038/nrn849>
- [25]. Thayer, J. F., & Lane, R. D. (2009). Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. *Neuroscience and biobehavioral reviews*, 33(2), 81–88. <https://doi.org/10.1016/j.neubiorev.2008.08.004>
- [26]. Krystal, J. H., Sanacora, G., & Duman, R. S. (2013). Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. *Biological psychiatry*, 73(12), 1133–1141. <https://doi.org/10.1016/j.biopsych.2013.03.026>
- [27]. Sinha R. (2024). Stress and substance use disorders: risk, relapse, and treatment outcomes. *The Journal of clinical investigation*, 134(16), e172883. <https://doi.org/10.1172/JCI172883>.