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REVIEW ARTICLE

Neuroimmune Interactions in Stress and Depression: Exploring the Molecular and Cellular Mechanisms within the Neuroinflammation-depression Nexus

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Abstract: ***Background*:** The escalating global burden of stress and depression underscores an urgent need to unravel their complex interrelationships and underlying mechanisms. This investigation delves into the intricate dynamics between stress and depression, spotlighting the Neuroimmunoinflammatory Stress Model (NIIS), which elucidates the pivotal role of cellular and molecular pathways in mediating these conditions.

***Methods*:** Through an exhaustive review of literature spanning epidemiology, neurobiology, and psychoneuroimmunology, this study synthesizes the current understanding of stress and depression. It accentuates the definitional scopes, interplay, and intricacies of the NIIS model, which integrates neuroimmune-inflammatory responses into the conceptual framework of the stress-depression interaction.

***Results*:** By identifying stress as a multifactorial reaction to perceived adversities and depression as a manifestation of prolonged stress exposure, our analysis foregrounds the NIIS model. This paradigmatic model reveals the transition from normal stress responses to pathological neuroinflammatory pathways, highlighting neurotransmitter imbalances, disruptions in neuronal and glial homeostasis, and ensuing low-grade neuroinflammation as key factors in the pathogenesis of depression under chronic stress conditions. The NIIS model identifies prolonged cellular pro-inflammatory stress of neurons and microglia as a fundamental pathological subsystem of many neuropsychiatric disorders. In turn, neuroinflammation and associated neurodegenerative processes are complications of chronic psychoemotional stress, which can clinically manifest as depression.

***Conclusions*:** The NIIS model views depression as the terminal stage of chronic stress, pathogenetically linked to latent neuroinflammation. This insight not only advances our understanding of their etiopathogenesis but also paves the way for developing precise therapeutic interventions.

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1. INTRODUCTION

1.1. Stress and Depression

1.1.1. Definitions of Stress and Depression

In the realm of contemporary pathology research, the interconnected phenomena of stress and depression are increasingly acknowledged for their profound impact on both individual health and societal structures. The escalating global prevalence of these conditions highlights the urgent need for a comprehensive understanding of their implications, symptomatology, and the intricate relationship between them [1]. This study aims to shed light on these aspects, underlining the importance of adopting multifaceted models to conceptualize and tackle these conditions, and proposes models for stress-depression interactions.

Stress, as delineated by Levine (2005) [2], defies a simplistic definition, embodying a complex construct that has been historically dissected from epidemiological, psychological, and biological perspectives [3]. The epidemiological view frames stress as a threats to social or physical well-being, the psychological perspective focuses on individual perceptions of stress, and the biological angle examines the physiological disturbances within the brain. Hans Selye (1976) offers a foundational definition of stress as the body's response to any demand, highlighting the physiological reactions triggered by both adverse and beneficial conditions [4]. This concept elucidates stress as the body's adaptive response to nonspecific demands, encompassing both negative (*e.g.*, starvation, infection) and positive (*e.g.*, foraging, mating opportunities) scenarios. The term 'stressor' signifies the actual or perceived threat, with the physiological reaction to it termed the 'stress response' [5].

The evolution of the stress concept underscores stressors as real or perceived threats to an organism's homeostasis, with a significant emphasis in the behavioral literature on perceptions of unpredictability and uncontrollability [6-10]. The stress response has been described as a general alarm within the homeostatic system [8], with suggestions to limit the term 'stress' to scenarios where environmental demands exceed an organism's regulatory capabilities [10]. Allostasis, introduced as an alternative to 'stress', refers to the process of achieving stability through a change in response to stimuli, encompassing both daily and seasonal physiological adjustments [11].

For the purposes of this study, we propose the following comprehensive definition of physiological stress: Stress is a multifaceted phenomenon characterized by the body's physiological and psychological response to perceived challenges or threats. It involves the activation of the HPA axis and the release of stress hormones like cortisol, reflecting the body's adaptation to demands [4, 7]. Psychologically, stress manifests as mental or emotional strain when environmental demands surpass an individual's coping resources without the additional mobilization of the body's extreme capabilities [12, 13]. Epidemiologically, stress is conceptualized as experiences and circumstances that are perceived as threats to well-being [3]. This definition acknowledges the diversity of stressors and emphasizes individual variability in stress perception and response, providing a broad yet nuanced framework for research across physiological, clinical, and psychological domains.

In the broadest sense, stress may be defined as the amplification of certain functions within biological and even biosocial systems beyond a state of relative rest, aimed at adapting to adverse changes in the internal or external environment.

Meanwhile, stress is psychologically defined as the response to internal or external stressors or conditions that challenge cellular or organismal homeostasis [14]. Depression is a complex psychiatric disorder characterized by neurochemical imbalances, altered brain structure and function, and genetic predispositions [15, 16]. It is diagnosed through criteria such as persistent sadness and changes in appetite and sleep patterns [17]. Psychologically, depression encompasses persistent negative feelings and cognitive symptoms like low self-esteem [18]. Unlike stress, traditionally understood as a reaction to an external trigger and variable in duration, depression represents a persistent state often devoid of a singular or identifiable external cause. The biological mechanisms distinguishing stress and depression involve immediate physiological adaptations for stress versus long-term neurochemical changes in the brain for depression.

However, the neurobiological overlap between stress and depression, characterized by alterations in neurotransmitter levels and brain activity patterns, underscores the intrinsic connection between these conditions. This interplay significantly affects both physical health and mental well-being, necessitating models that encompass biological, psychological, and social dimensions to fully understand the stress-depression nexus. Seminal works, such as those by Kessler (1997) and McEwen (2000), among others, highlight the complexity of the relationship between life events, stress, and depression, advocating for integrative models that consider a wide array of factors [19, 20].

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Moreover, the contributions of Michael Maes from 1995 have been pivotal in elucidating the biological aspects of depression, particularly the role of inflammation and the immune system in its pathophysiology [21-23]. This body of work enriches our comprehension of depression by integrating biological, psychological, and environmental perspectives, paving the way for novel approaches to understanding and treating this disorder.

1.1.2. The Intersections Between Stress and Depression

One of the most critical intersections between stress and depression is the role of stress as a potential precursor or trigger for depression. Numerous studies have demonstrated that prolonged or intense stress can precipitate the onset of depressive episodes, suggesting a causal relationship in certain cases [24, 25]. With this understanding, depression can be conceptualized as a complex and severe manifestation of stress. While stress is a response to perceived threats or challenges, resulting in physiological and psychological strain, depression arises when these stress responses become chronic or overwhelming. It represents a state where the body's and mind's ability to cope with prolonged stress is compromised, leading to a range of symptoms such as persistent sadness, loss of interest, and cognitive changes. This perspective aligns with the concept of allostatic load, which refers to the cumulative burden of chronic stress and life events on the body's physiological systems [26-28]. Over time, this allostatic load can lead to significant health problems, including depression. In the context of depression, allostatic overload signifies a point at which the body's mechanisms for coping with stress fail to function properly due to the excessive burden of stress. This can result in the dysregulation of neurotransmitters, hormones, and inflammatory pathways that are implicated in depression. Therefore, depression, when viewed through the lens of stress and allostatic load, is not merely a psychological condition but a multifaceted disorder that encompasses biological, psychological, and social dimensions.

At the same time, any complex process in biological systems involves mechanisms of self-regulation that limit its development, including negative feedback mechanisms. Overall, this forms an inherently contradictory system, whose characteristic feature is the functional unity and opposition of divergent processes. The dominance of activation or suppressive mechanisms is generally relative and conditional, usually subordinated to solving specific clinical tasks.

When suppressive mechanisms, due to dysregulation or damage to activation mechanisms, exert a determining influence on key parameters of the pathological process, one can speak of the presence of clinically significant depression. When suppressive mechanisms, due to dysregulation or damage to activation mechanisms, exert a determining influence on key parameters of the pathological process, one can speak of the presence of clinically significant depression (neuropsychiatric, neuromuscular, immune, neuroendocrine distress, *etc.*). From this perspective, depression can be viewed as the terminal stage of chronic stress, namely, the stage of neuropsychic exhaustion, which has a maladaptive rather than an adaptive significance. The functional heterogeneity of cognitive and other forms of stress is determined by the following general biological systemic patterns.

Firstly, the response of various biological systems to adverse changes can manifest as two often interrelated strategies: active resistance and passive tolerance toward the action of the damaging agent.

Secondly, both hyperergic activation and hypoergic depression do not manifest totally but rather mosaically. In particular, mental depression is associated in the brain not only with the presence of atrophy zones but also with divergent activity patterns of neurons in various brain regions [29, 30]. Additionally, the depression of some functional parameters of the system may accompany the hyperactivity of others, for example, mental depression typically features an elevated blood level of cortisol - a key indicator of hypothalamic-pituitary-adrenal axis activity [31, 32]. Meanwhile, experimental and clinical studies indicate that psychological traumas and certain forms of depression can lead to adrenal hypofunction [33, 34].

Thirdly, depression and hyperactivity may have a phase-specific character, for example, in manic-depressive syndrome [35].

Finally, a persistent depressive state may be a stage of a more complex process, initially involving a phase of hyperactivity. Specifically, acute inflammation can transition into chronic inflammation with signs of immunological suppression [36]. Life-threatening systemic inflammation in its early stages is characterized by a cytokine storm. However, a critical but more temporally stable depressive phase of this process, with moderate cytokinemia manifestations, can subsequently develop. This transition depends on the intensity of systemic damage (*e.g.*, sepsis, acute trauma) and the severity of the initial hyperergic response. Usually, the depressive phase of systemic inflammation develops several days or weeks from the onset of the critical con-

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dition [37] and in the case of an ultra-acute process - within a few hours [38]. This pattern may be universal, including the relationship between psychogenic stress, depression, and other mental illnesses [39, 40].

Thus, from the perspective of general pathology, psychogenic depression can be considered both a complication of stress and, as its stage, associated with the transition from adaptive stress to maladaptive distress. However, we believe it is appropriate to leave the final resolution of this issue to clinicians, primarily psychotherapists and psychiatrists.

The rationale for the current study is to provide a comprehensive understanding of the molecular and cellular mechanisms linking chronic stress and depression. By focusing on the NIIS model, this study aims to elucidate the neuroimmune-inflammatory pathways that mediate the transition from normal stress responses to pathological neuroinflammation, ultimately contributing to depression. This insight is intended to pave the way for developing precise therapeutic interventions targeting these pathways.

1.1.3. Two Alternative Causes and Two Interrelated Directions of Stress Development and Their Association with Inflammation

Excluding the stress of social and ecological systems, as well as the neuromuscular behavioral aspects of biosocial stress, from the current analysis necessitates a detailed examination of the cellular, organ, tissue, and systemic processes underlying the physiological and pathological manifestations of stress and depression. This includes neuroendocrine stress related to higher nervous activity and various types of cellular-tissue stress associated with inflammation. Hans Selye conceptualized stress as an organism-level event, initially linked to the activation of the neuroendocrine system, followed by the response of other organs to external stimuli. Psychoemotional stress, following neuroendocrine stress initiation, facilitates adaptation to external changes through both nonspecific organ activity to external influences and selectively targeted neuromuscular activity. Simultaneously, Selye identified inflammation as a variant of the local (tissue) adaptation syndrome [41]. In this context, unlike cognitive stress, pro-inflammatory tissue stress is primarily aimed at addressing internal homeostatic issues ("internal stress"), where these two stress variants may share common functional components.

As understood today, the systemic inflammatory response develops at the organismal level, including as a form of neuroendocrine stress, that is, the activation of the hypothalamic-pituitary-adrenal axis, similar to stress aimed at addressing external problems [42-44]. This second or "internal" stress variant focuses on resource provisioning for inflammation and immune response processes. However, its characteristic feature also includes neuromuscular asthenia and, in some cases, neuropsychiatric depression [21, 22, 45, 46]. This pattern is also evident in systemic endocrine-metabolic dysfunctions, such as type 1 diabetes [47] and cancer diseases [48]. Thus, addressing "internal problems" may hinder the performance of "external tasks" related to neuromuscular activity, contributing to the maladaptation of "external" stress.

Cellular stress, an elementary yet holistic functional unit of tissue ("internal") stress, can be defined as "Cellular pro-inflammatory stress: a complex of interrelated universal and specific (to specific populations) cell processes in response to the action of factors of real and potential damage" [49]. A fundamental principle is that tissue and, more so, cellular stress should not be associated solely with inflammation [50]. If one were to metaphorically represent all manifestations of tissue stress as an iceberg, canonical inflammation (the presence of characteristic signs of an inflammation focus) would only be the tip of this complex, multi-level formation (Fig. **1**). The less visible, underwater part of the "iceberg" encompasses not only non-classical variants of inflammation or low-grade inflammation but also many physiological processes, including embryogenesis, muscle work, normal processes of immunogenesis, among others. Furthermore, pro-inflammatory mechanisms, as a kind of pro-inflammatory tone, are embedded at the cellular level in the normal (non-extreme) physiological processes of many cell types, especially the epithelia of the covering tissues [50]. In this sense, some authors define the condition of normal intestinal mucous membranes as "physiological inflammation" [51]. However, we believe that such an approach does not align with the methodological canons of general pathology and pathological physiology.

In this case, it is more appropriate to speak of the physiological importance of tissue stress as a common platform for various pathological and physiological processes and states. Herein, for immunocytes, pro-inflammatory stress is directly linked to their primary specialized functions. For most other cells, stress is more likely a typical extreme reaction, which complements, but often hinders, the performance of their specialized functions.

Thus, the execution of specialized functions, even under physiological conditions, leads to the accumulation of molecular-cellular and tissue damage, necessitating the involvement of mechanisms for addressing

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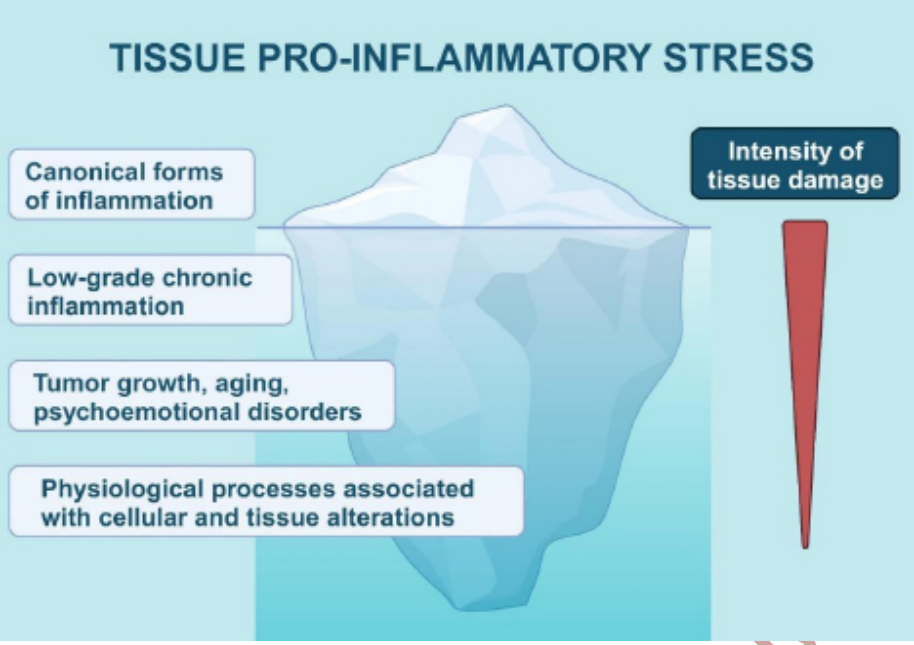

Fig. (1). The Integrative Role of Tissue Stress (the "Iceberg" Model) in Various Pathological and Extreme Physiological Processes. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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homeostatic problems and pro-inflammatory cellular and tissue stress mechanisms.

1.1.4. Stress and Distress

Determining the pathological threshold of a stress response presents a considerable challenge. Traditionally, stressors are defined as stimuli that disrupt or threaten to disrupt homeostasis [52], but this perspective is not without limitations [53]. A more expansive definition views stressors as unpredictable and/or uncontrollable stimuli [6], encompassing a broader spectrum of stress-inducing conditions.

From a pathophysiological point of view, genetically programmed mechanisms of pro-inflammatory stress are protective but only within the limits of their intensity, duration, tissue localization, and balance with other processes. Deviation from these parameters may transform the "cure" into "poison," with stress-dependent mechanisms becoming key players in maladaptive, dysfunctional systems, thereby contributing to the pathogenesis of various diseases. In particular, psychological stress can impact somatic health directly through autonomic and neuroendocrine reactions, as well as indirectly through health-related behavioral changes [54]. In such instances, cognitive stress can transform into distress [55].

It is important to acknowledge that integrated stress processes in pathology involve various components, including those of adaptive value. In contrast, potentially maladaptive stress mechanisms can manifest even within physiological processes. Furthermore, the same specific stress mechanism may exhibit adaptive and maladaptive properties in different processes, and the pathogenetic role of the latter is not always clearly assessable and separable from pathogenetic factors of a different nature. Given these considerations, some authors question the practicality of distinguishing stress from beneficial eustress and pathological distress [56].

Our stance on this issue is as follows: in all ambiguous cases, it is preferable not to differentiate the term stress into eustress (beneficial stress) and distress. However, when the role of stress in the development of pathology is evident and consistent, it is appropriate to characterize it as distress. Examples include the association between psychogenic stress and hypertension in clinical and experimental settings [57, 58], as well as the classic triad of distress: atrophy of the adrenal and lymphoid organs, stress ulcers [42], and the consistent link between psychogenic trauma and depression [24].

2. STRESS/DEPRESSION HYPOTHESES AND MODELS

To unravel the intricate nexus between stress and depression, an array of models provides distinct but complementary perspectives. These models elucidate

the multifaceted interactions between genetic, biological, environmental, psychological, and social factors in the genesis of depression.

The Diathesis-Stress Model posits that depression results from the interaction between an individual's vulnerability (due to genetic or biological predispositions) and environmental stressors. This model underscores the synergy between inherent susceptibilities and external challenges in precipitating depressive episodes, offering a holistic understanding of the etiological landscape of depression [59-101].

The Biopsychosocial Model broadens this conceptualization by incorporating psychological and social dimensions. It acknowledges the significant roles of cognitive processes, personality traits, and social support systems, thus providing a more comprehensive framework that captures the complex interplay of biopsychosocial factors in the development of depression [13, 61, 77-79].

Allostatic models focus on the physiological adaptations of the body in response to stress. These models highlight how chronic stress can lead to an allostatic load, a state of physiological wear and tear, which potentially predisposes people to depression by affecting physiological resilience and contributing to the breakdown of regulatory systems [7, 11, 80].

This review systematically categorizes these models into three overarching conceptual frameworks: the Diathesis-Stress, Biopsychosocial, and Allostatic Models (Table **1**). However, it becomes evident that while these models illuminate the roles of individual neurotransmitters and their receptors, they do not provide a holistic understanding of the pathogenesis of depression. The critique herein lies in the observation that the detailed mechanisms involving neurotransmitters and their numerous receptors, as addressed by current models, do not fully capture the comprehensive pathophysiological landscape of depression.

2.1. The Diathesis-stress Framework

The Diathesis-Stress Model, fundamental in psychological research, elucidates the onset of psychological disorders through the interplay between individual vulnerabilities and environmental stressors [75, 84-86]. It proposes that predispositions - genetic, biological, or personality related - require external stress activation, such as traumatic or chronic adversities, to manifest mental disorders. Reflecting on recent advances, studies have expanded the application of the model, exploring its relevance in various contexts, including depression in young people and historical perspectives of mental illness, thus underscoring its sustained significance [75, 84-86].

Furthermore, the model integrates the influence of social environmental factors, although it faces limitations in fully capturing the complexities of depression's pathogenesis. This critique emphasizes the necessity of a broader exploration of contributing factors to mental health disorders.

Building on this, the framework considers associated models like the Monoamine Hypothesis and the GABAergic Hypothesis. The Monoamine Hypothesis, for example, posits that depression and stress-related disorders stem from the depletion of key neurotransmitters, laying the groundwork for SSRIs [59-61]. However, the complexity of depression's neurobiology suggests that a multitude of factors are at play.

Delving further, the "Disruption of the Long Neuronal Chain of Monoamines" model and the hypothesis linking prolonged cortisol secretion with depressive behavior offer deeper insights into the neurobiological mechanisms of depression, highlighting the roles of cortisol and serotonin imbalances [62-65]. Similarly, the GABAergic Hypothesis suggests that disruptions in GABAergic transmission could underpin depression, underscoring the disorder's complexity and the necessity for a comprehensive approach [66-68, 88].

Additionally, the Glutamate and Neuroplasticity Hypothesis connects depressive disorders to reduced neuroplasticity and morphological changes in hippocampal neurons, emphasizing the critical role of the glutamatergic system [61, 69, 89-93]. This focus on glutamate excitotoxicity and neuroplasticity offers significant insights but may not fully address the multifaceted nature of the disorder. Moreover, the Hypothesis of Impaired Neurogenesis in the Dentate Gyrus suggests a link between reduced neurogenesis and depressive symptoms, with stress potentially exacerbating this impairment [69, 71, 94, 95]. This perspective provides valuable insights but may overlook other contributing factors to depression's complexity.

Finally, the Neurotrophic Hypothesis attributes depression's pathophysiology to compromised neurotrophic support, affecting synaptic plasticity and neural network health [72, 96-101]. While offering a compelling framework, it highlights the necessity for integrated treatment approaches that consider the broad etiology of the disorder.

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Table 1. Overview of Hypotheses on Stress, Depression, and Their Interplay.

Hypothesis	Description	References
The Diathesis-Stress framework		
Neurotransmitter-Based Hypotheses		
Monoamine Hypothesis	Suggests that stress and depression pathogenesis is primarily due to the depletion of brain monoamine neurotransmitters, such as serotonin, norepinephrine, and dopamine.	[59-61]
Disruption of the "Long Neuronal Chain of Monoamines"	Both monoaminergic and nonmonoaminergic mechanisms are critical, forming an extensive neural circuit responsible for rapid synaptic plasticity. Disruption can result from genetic factors.	[62,63]
Prolonged secretion of cortisol as a possible mechanism underlying stress and depressive behaviour	Chronic stress leads to increased cortisol secretion, contributing to depression.	[64]
Cortisol, serotonin and depression	Major depression linked with decreased brain serotonin function and elevated cortisol secretion.	[65]
The GABAergic Hypothesis	Altered GABAergic transmission could underpin depression, exacerbated by stress.	[66-68,88]
Neuroplasticity and Neurogenesis Hypotheses		
Glutamate and Neuroplasticity Hypothesis	Depressive disorders result from reduced neuroplasticity and dysregulation due to glutamate excitotoxicity.	[61,69,89-93]
Neuroplasticity Hypothesis	Morphological changes in hippocampal neurons contribute to reduced hippocampal volume in depressive disorders.	[70,99]
Hypothesis of Impaired Neurogenesis in the Dentate Gyrus of the Hippocampus	Impaired neurogenesis in the dentate gyrus may lead to reduced hippocampal volume in depressive disorders.	[69,70,71, 94,95]
Neurotrophic Hypothesis	Changes in synaptic plasticity in depression due to impaired neurotrophic support.	[72-74, 96-101]
Biopsychosocial framework		
Biopsychosocial Model	Integrates biological, psychological, and social factors in understanding health and illness.	[76,102-104]
Stress-Related Hypotheses:		
Stress, Coping, and Depression Hypotheses	Examines the relationship between stress, coping, and depression, including protective factors.	[61]
Stress-buffering hypothesis	Social support mitigates the adverse effects of stress, acting as a protective buffer that diminishes the negative psychological and physiological impacts of stress.	[77,78,113,114]
Stress-Vulnerability-Coping Model	Interaction between vulnerability, stress, and coping mechanisms.	[79]
Transactional Model of Stress and Coping	Focus on individual perception and coping with stress.	[13]
Allostatic framework		
Allostasis	Chronic stress leads to physiological and psychological maladaptations, contributing to depression.	[7,11,26-28,80,105-112]
Other		
Neurogenic Hypothesis of Positive Psychology in Stress-Induced Depression	Adult hippocampal neurogenesis (AHN) participates in the stress response, influencing memory and stress-induced depression.	[70,115]
The Gut-Brain Hypothesis	Emotional stress and poor dietary habits can drive pathological changes in the gut microbiome, affecting mental health.	[81-83]

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In summary, these hypotheses collectively underscore the complexity of depression, advocating for an integrative research and treatment approach that encompasses the multifaceted nature of the disorder. This includes exploring beyond single neurotransmitter systems to a comprehensive understanding of genetic, environmental, and psychological influences.

2.2. The Biopsychosocial Framework

The Biopsychosocial Model is a comprehensive approach for understanding health and illness, transcending the traditional biomedical model by integrating biological, psychological, and social factors [76, 102-104]. This model emphasizes that health is not solely the absence of disease or infirmity but a dynamic state of complete physical, mental, and social well-being. It posits that biological factors (such as genetic predispositions and immune system function), psychological factors (including thoughts, emotions, and behaviors), and social factors (like cultural influences, family relationships, and social support) all play a significant role in human functioning in the context of disease or illness. According to the Biopsychosocial model, these three domains interact with one another in complex ways to influence health outcomes. For example, a person's mental health can affect physical health (psychological domain that influences the biological domain), while social norms and relationships can impact psychological well-being (social domain influencing the psychological domain) [76, 102-104].

2.3. The Allostasis Framework

The Allostatic Model explores how chronic stress leads to physiological and psychological impacts that contribute to depression, emphasizing the concept of allostatic load as the cumulative burden of chronic stress on the body. Originally proposed by McEwen and Stellar, this concept has been instrumental in understanding depression's development [26-28]. Subsequent research, including the work of Juster *et al.*, has quantified the allostatic load, highlighting its relevance to mental health and its potential as a psychiatric marker [27, 105-107]. Further investigations by Gianaros and Wager have detailed the effects of chronic stress on key brain regions involved in stress and emotional regulation, linking these changes to an increased risk of depression [108, 109]. The research of Ganzel, Morris and Wethington illustrates how chronic stress alters the hippocampus, amygdala, and prefrontal cortex, areas vital to mood, cognition, and mental health. These alterations affect neurotransmitter systems, hormone levels, and neural plasticity, enhancing susceptibility to stress and psychiatric disorders such as depression [110].

Additionally, studies examining allostatic load's interaction with external factors such as socio-economic status and early-life trauma, by Danese and McEwen, underscore depression's complex nature [111].

However, while the Allostatic Model provides valuable insights into stress's biological effects, it calls for a more comprehensive approach that includes psychological resilience, social support, and environmental influences. From a broader pathological perspective, allostasis represents a stable and relatively persistent change in homeostasis, pathogenetically linked to various chronic systemic pathologies, primarily metabolic syndrome and age-related changes leading to low--grade chronic systemic inflammation. This connection with depression is multifaceted, diverse, and non-specific, often associated with systemic low-grade inflammation seen in older individuals with comorbid conditions that may precede depression. Therefore, the formation of stable allostasis in depression is not always present, and when it is, it forms a pathogenetic vicious circle, making it challenging to determine the specific contribution of depression to allostatic formation.

2.4. Other Stress Models

The Stress, Coping, and Depression Hypotheses explore the dynamic interplay between stress exposure, coping mechanisms, and depression risk, suggesting the pivotal role of effective coping strategies as protective factors [61]. Although insightful, this approach primarily emphasizes psychological over biological factors, potentially overlooking depression's complex etiology and the challenge of standardizing stress perception and coping effectiveness.

Moreover, the Stress-Buffering Hypothesis, highlights social support's protective role against stress's psychological impact, underscoring the value of robust social networks in mitigating stress-related mental health issues [112, 113]. However, this model's emphasis on the social and psychological may not fully account for individual biological responses and the subjective nature of perceived social support.

The Neurogenic Hypothesis of Positive Psychology in Stress-Induced Depression introduces a biological foundation for positive interventions through adult hippocampal neurogenesis (AHN), suggesting a novel avenue for depression mitigation [70, 114]. Despite its potential, the hypothesis faces challenges in clarifying the pathways through which increased neurogenesis improves mood and resilience.

Furthermore, the Gut-Brain Hypothesis emphasizes the bidirectional relationship between gut health and

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mental well-being, proposing that interventions targeting the gut microbiome may offer new treatment avenues [81-83]. However, the complexity of this relationship and the challenge of delineating specific mechanisms underscore the need for further research.

In summary, these models collectively enhance our understanding of the etiology of depression from various angles, emphasizing the need for an integrative approach that combines psychological, biological, and social perspectives to address the complexities of mental health comprehensively.

3. CELLULAR AND TISSUE STRESS SERVES AS THE FOUNDATIONAL BASIS FOR THE GENERAL PATHOLOGICAL PROCESSES

Cellular and tissue stress serves as the foundational basis for the general pathological processes observed in various human diseases. This understanding is structured across three principal levels of medical consideration: personalized medicine, which focuses on individual patient pathology; standard clinical protocols and models for disease classifications; and the overarching models of general pathological processes, which, while not clinical definitions themselves, fall within the realms of general pathology and pathophysiology. Some tasks at this third level are addressed by conceptual syndromes, which essentially act as surrogate forms of general pathological processes.

Abstract models of typical pathological processes holistically characterize the main pathogenetic patterns, thus differentiating pathologies into distinct classes. The most integrated forms of these processes include tumor growth and both canonical and non-canonical forms of inflammation. Canonical (classic) inflammation, characterized by the presence of an inflammatory focus that serves as a barrier function against damaging factors, is primarily mediated by the inflammatory response of microvessels, migrant leukocytes, and monocyte-originating inflammatory macrophages. Depending on the balance of exudation, migration, and proliferation of specific leukocyte populations, the degree of tissue destruction, and the nature of the damaging factor, canonical inflammation is divided into more specific types and subtypes [50]. At a certain intensity, the inflammatory focus process escalates into a systemic inflammatory response, which, in the case of classical inflammation, is overall protective, providing resources for the processes at the inflammation focus and organs involved in systemic-level inflammatory reactions.

Systemic hyperinflammation, not necessarily related to an inflammation focus, is characterized by critically strong systemic effects of damaging factors leading to a systemic inflammatory reaction in microvessels of vital internal organs, disseminated intravascular coagulation, a cytokine storm, and ultimately life-threatening microcirculatory disorders in patients [50]. Low-grade inflammation or para-inflammation, not marked by significant local damage and thus signs of an inflammation focus, can relatively easily generalize within the body, leading to stable allostasis. It arises in response to moderately severe damaging factors, including metabolites (meta-inflammation, especially in morbid obesity, metabolic syndrome, and type 2 diabetes) [115, 116], tissue aging (inflamm-aging) [117, 118], and the generalization of moderate amounts of endotoxin (LPS) and other intestinal toxins with impaired intestinal barrier and microbiome [119]. Low-grade inflammation is characterized by moderate cytokinemia, dyslipoproteinemia, insulin resistance, signs of endotheliosis, indications of immune system discreditation, a significant pathogenetic role of stromal macrophages and scavenger receptors, and the presence of degenerative changes in various organs, including neurodegeneration [50].

Transformation of one general pathological process into another is possible, for example, decompensated classical inflammation may be complicated by systemic hyperinflammation, and local low-grade inflammation, with its progression, may acquire characteristics of an inflammation focus [49]. Some processes, such as atherosclerosis, may occupy an intermediate position between low-grade inflammation and classical inflammation. Therefore, atherosclerosis can be characterized as a distinct form of a general pathological process, simultaneously incorporating phenomena of low--grade inflammation and classical inflammation [120].

Thus, the functional foundation of virtually all major types of general pathological processes, and even extreme physiological processes, is tissue pro-inflammatory stress, with cellular stress as its elementary functional component (Fig. **2**).

More specific processes at the tissue level include oxidative stress, cytokine network formation, atrophy, tissue aging and sclerosis, tissue regeneration, tissue degeneration, and at the cellular level, various forms of programmed cell death (apoptosis, cell necrosis), cellular oxidative stress, DNA damage response, mitochondrial unfolded protein response (UPR), stress of the endoplasmic reticulum, including calcium-dependent mechanisms and UPR, autophagy, inflammasome formation, and regulatory noncoding RNAs, forming an inducible pro-inflammatory receptor and secretory phenotype of various cell types [121]. These processes

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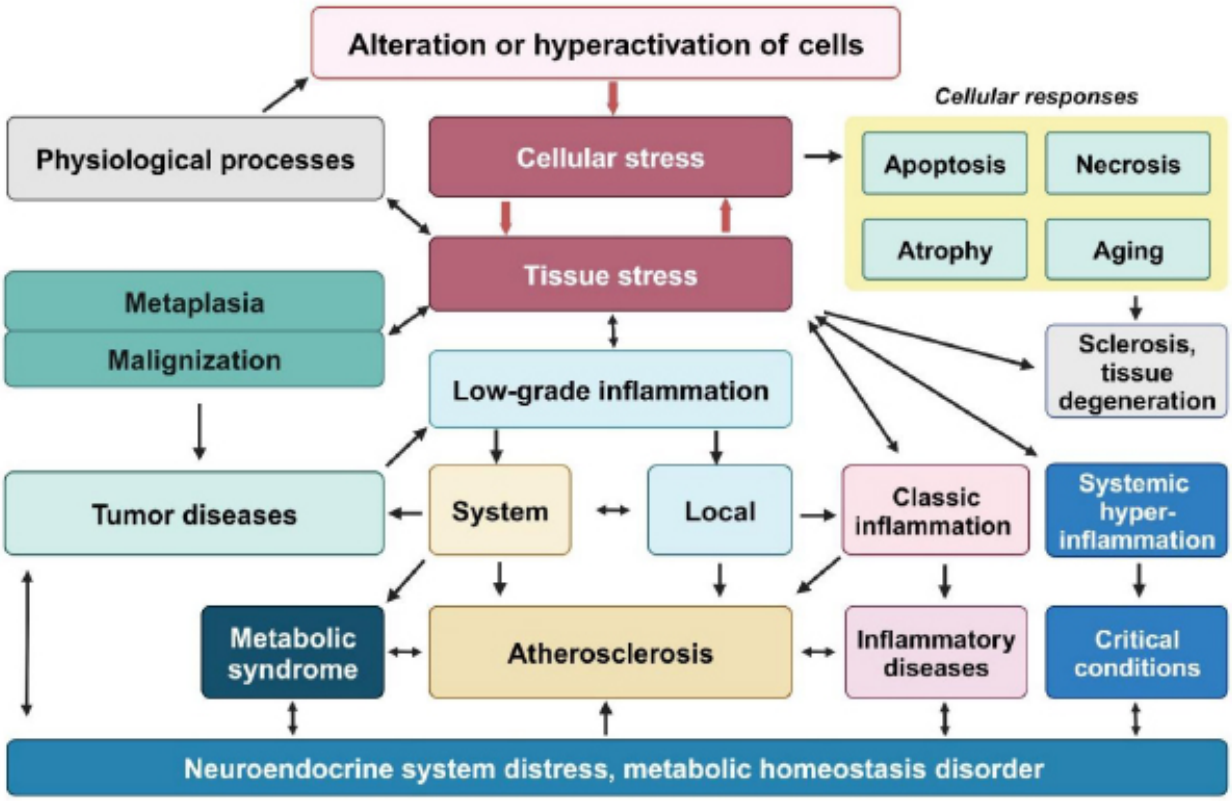

Fig. (2). Schematic model of cell and tissue stress as a common platform for various human pathologies. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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are integrated with each other and with various metabolic processes through a network of signaling pathways. Different extracellular and intracellular stress signals can activate in various cells the common protein kinases of the collector type (*e.g.*, MAPK, AKT, PI3K, PKC, ATM, ATR, AMPK, PKA, PKR, mTOR) and key universal transcription factors of cellular stress (*e.g.*, NF-κB, p53, AP-1, HIF, HSF, NRF2, ATF4, STAT) [Gusev, 2019].

Given the above, a fundamental question arises about the possibility of incorporating depression and many other mental disorders into the general system of typical pathological processes.

4. THE NEUROIMMUNE-INFLAMMATORY MODEL OF CHRONIC STRESS/DISTRESS AND DEPRESSION ASSOCIATED WITH PSYCHOGENIC STRESS

4.1. Definition

The Neuroimmune-Inflammatory model of chronic stress/distress and depression associated with psychogenic stress defines the diverse and often divergent dysfunctions of various neurotransmitters, homeostatic changes in neurons and glial cells, and morphofunctional changes at different brain regions as based on typical dysfunctional processes of cellular and tissue pro-inflammatory stress (Fig. **3**). The escalation of these processes leads to low-grade neuroinflammation, promoting neurodegenerative changes and making the pathological process difficult to reverse. Local pro-inflammatory changes in the brain during depression can create a vicious pathogenetic cycle with systemic chronic low-grade inflammation, forming a stable allostatic state at the organism level.

4.2. Physiological Mechanisms of Cellular and Tissue Stress as Pathogenetic Risk Factors for the Onset of Low-grade Neuroinflammation in Chronic Stress and Depression

The key factors in the pathogenesis of depression under chronic stress conditions, according to the NIIS model, include neurotransmitter imbalances, disruptions in neuronal and glial homeostasis, and low-grade neuroinflammation. Prolonged cellular pro-inflammatory stress in neurons and microglia, as well as the subsequent neurodegenerative processes, play critical roles in the development of depression.

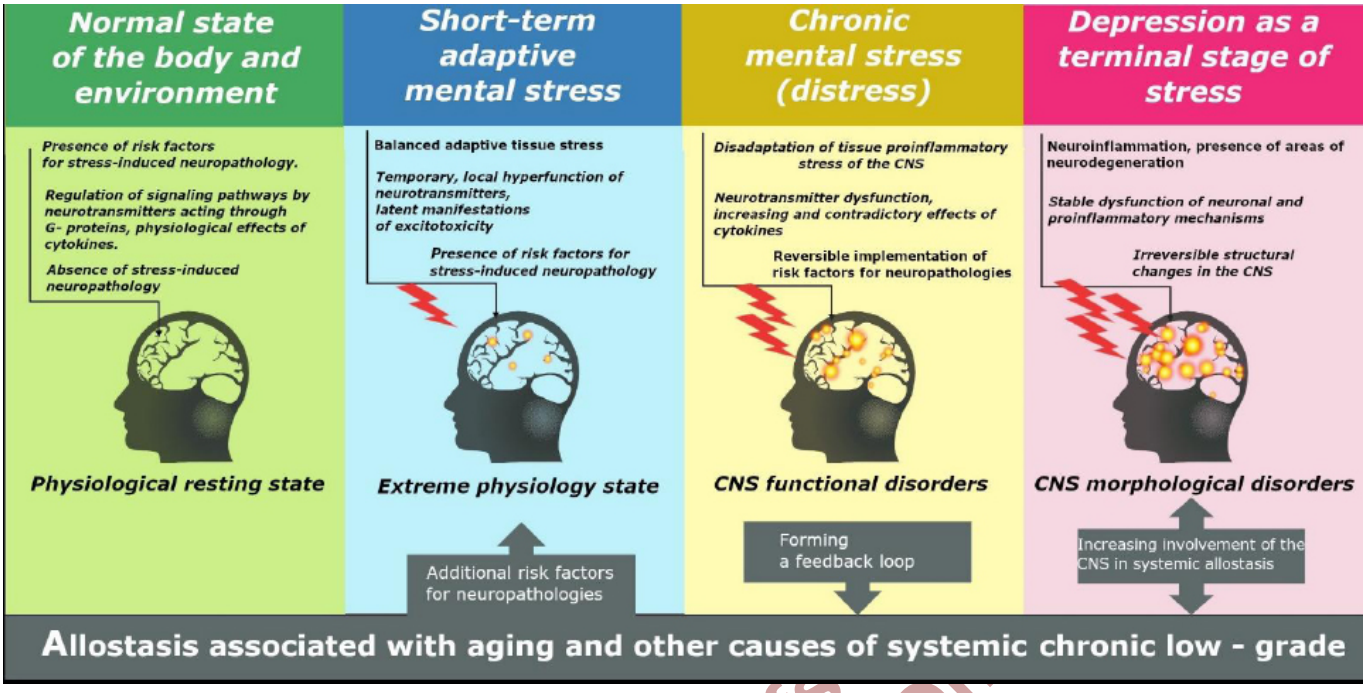

Fig. (3). The neuroimmune-inflammatory concept (model) of chronic stress/distress and depression associated with psychogenic stress. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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Already in physiological conditions, the function of brain neurons is at risk of damage and even programmed death due to the development of cellular stress. This is due to certain characteristics of nervous tissue that predispose it to physiological pro-inflammatory tone and the risk of its progression to pathological neuroinflammation:

- Instability of electrolyte balance and membrane potential related to the receptor effects of neurotransmitters.
- A high specific level of constant basic energy consumption for aerobic ATP production (the brain, constituting ~2% of the body, consumes ~25% of oxygen in norm), indicating a high dependence of neurons on mitochondrial stress.
- High tension in basic protein biosynthesis, indicating a high dependence of neurons on endoplasmic reticulum stress.
- High sensitivity of the proteome and cell membranes to the damaging effects of oxidative stress.

In response to the intensification of damaging factors, cellular stress develops aimed at mitigating these factors and restoring homeostasis. However, when cellular stress becomes chronic and unbalanced, it transforms into a dysfunctional process that exacerbates cellular damage, for example, through poorly balanced oxidative stress. In turn, the main mechanisms for regulating and limiting pro-inflammatory cellular stress in the brain include:

- The presence of the blood-brain barrier.
- The CNS does not use higher fatty acids for aerobic ATP formation in mitochondria, reducing the likelihood of lipotoxicity.
- More stringent maintenance of key homeostasis parameters in the CNS, including oxygen and glucose levels.
- Microglia, which are relatively inactive macrophages in the human body.
- Cellular stress and metabolism in neurons are regulated by neurotransmitters acting through metabotropic receptors linked to G-proteins (G-PCR).

Neurotransmitters operate through two types of receptors: ionotropic receptors, which are ion channels, and metabotropic receptors, known as GPCRs. Hyperactivity of neurotransmitter receptors can become excitotoxic, leading to neuron damage. This is particularly understood regarding postsynaptic glutamatergic ionotropic receptors (NMDAR1-3) that selectively bind N-methyl-D-aspartate (NMDA). GPCRs can indirectly regulate the function of ion channels and also

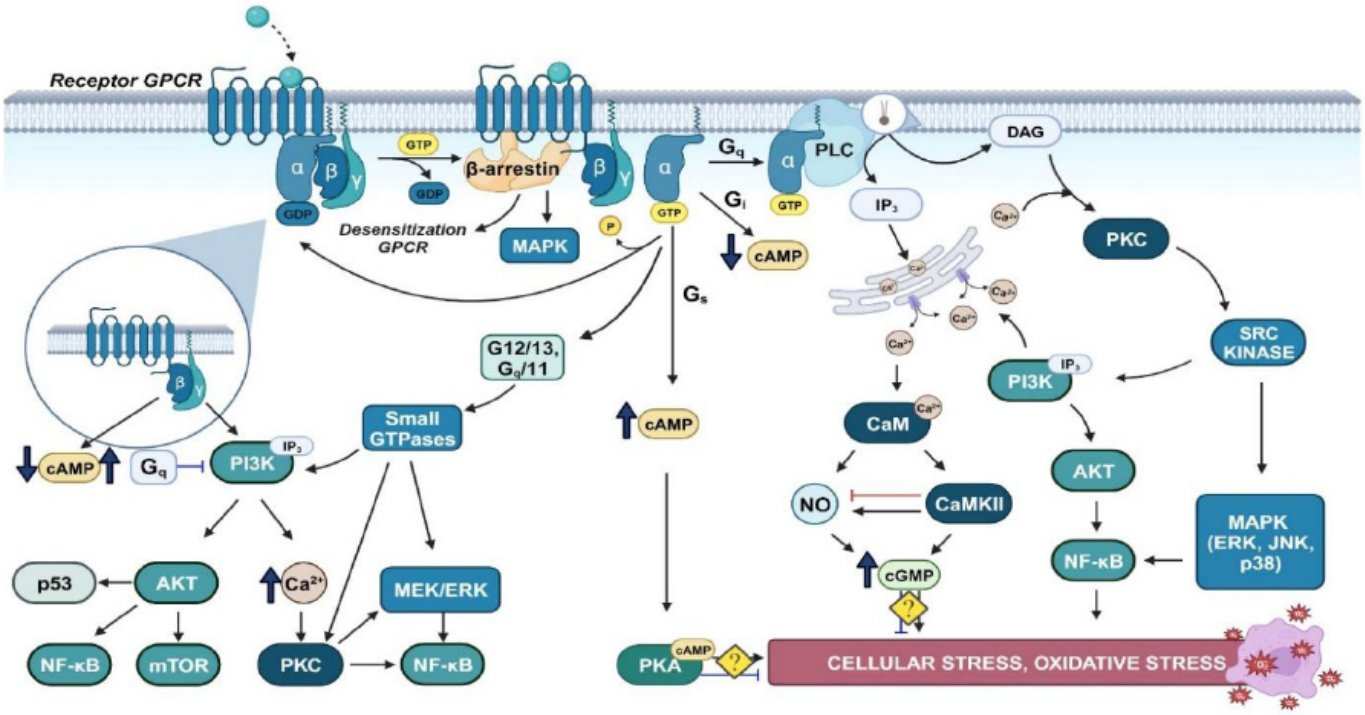

Fig. (4). The Role of GPCR Receptors in Cellular Stress Development [122]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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control metabolic processes, including through well-known cellular stress signaling pathways (Fig. **4**). Thus, various factors, primarily excitotoxicity, can initiate the development of pro-inflammatory cellular stress in neurons, with GPCRs acting as regulators of not only cellular metabolism but also cellular stress.

This figure illustrates the complex mechanisms through which GPCRs contribute to cellular stress. Upon ligand binding, GPCRs interact with trimeric G proteins (αβγ), leading to GDP-GTP exchange on the Gα subunit and its subsequent dissociation and activation. The cycle completes with GTP hydrolysis and reassociation of the Gα subunit with Gβγ, inactivating the G protein. The G proteins are categorized into four families—Gs, Gi, Gq, and G12/13—each triggering distinct signaling pathways. Gs activates adenylate cyclase, increasing cAMP levels and PKA activity, while Gi inhibits this process. Gq stimulates PLC, generating IP3 and DAG, which release Ca2+ and activate PKC. This cascade influences various stress pathways, including PKC/MEK/ERK, PKC/Sc/MAPK, and PKC/Sc/PI3K/AKT. PI3K signaling, vital for cell stress responses, can be activated by Gα/PKC, Gα/small GTPases, and Gβγ, affecting cell cycle, proliferation, and apoptosis. Adenylate cyclase, modulated by Gs or Gi, produces cAMP that activates PKA, generally exerting anti-inflammatory effects. However, the specific impact of cAMP on cellular stress is complex. Calcium, calmodulin, and CaM kinases also play roles, impacting NO production and cGMP formation. Additionally, small GTPases (*e.g.*, Ras, Rho, Rab) activated by G12/13 and Gq modulate signaling through PI3K, ERK, and AKT. Finally, GPCRs can activate MAPK *via* β-arrestin, which also mediates GPCR desensitization and internalization, illustrating the intricate regulatory network of GPCRs in cellular stress mechanisms.

Most neurotransmitters indeed interact with several types of G protein-coupled receptors (GPCRs), activating various Gα subunits, which illustrates the complexity and versatility of signaling mechanisms within the nervous system [122]. For instance, serotonin interacts with multiple receptor subtypes, including 5-HT1 through 5-HT7, each linked to different G proteins that mediate diverse physiological responses. Similarly, norepinephrine and epinephrine can signal through β1-AR, β2-AR, α1-AR, and α2-AR, affecting various cellular outcomes. Dopamine, glutamate, γ-aminobutyric acid (GABA), acetylcholine, substance P, neurokinin, endo-opioids, and endocannabinoids also demonstrate this multiplicity of receptor interactions, indicating a broad spectrum of effects ranging from neurotransmission to cell signaling [122]. Moreover, the role of

GPCRs is not limited to neurotransmission but extends to the immune response, where many inflammatory mediators also utilize these receptors. For instance, complement component C5a, prostaglandin E2, leukotrienes D4 and E4, histamine, bradykinin, thrombin, angiotensin II, platelet-activating factor, endothelin, extracellular ATP, adenosine, chemokines, lysophosphatides, and bacterial formyl peptides all engage with GPCRs to mediate their effects [122].

The shared mechanisms of GPCRs for neurotransmitters and immune/inflammatory mediators underscore the immunotropic effects of almost all neurotransmitters acting beyond the nervous system. Glial cells, including the cytokine-dependent effects of microglia, can serve as physiological regulators of cellular stress. Specifically, the action of cytokines on neurons may be mediated by universal cellular stress signaling pathways: JAK/PI3K/AKT, JAK/STAT, MAPK/NF-κB [122, 123]. Therefore, moderate, short-term cellular stress, as well as a more stable pro-inflammatory tone, is essential for maintaining homeostasis in neurons under both normal and extreme physiological conditions.

4.3. Pathological Manifestations of Tissue Stress and the Development of Low-Grade Neuroinflammation in Morbid Psychological Stress and Depression

In physiological conditions, the pro-inflammatory tone of tissue and extreme physiological tissue stress can transform into a dysfunctional, maladaptive process under the imbalance of pro-inflammatory mechanisms, akin to psychological stress. Cellular and tissue phenomena in this process include dysfunction, damage, and death of neurons, leading to areas of neurodegeneration and accelerated brain aging typical of depression associated with neuroinflammation [124-126]. During this negative dynamic, an increasing pathogenetic role of cytokines and other inflammation mediators is observed [123-127]. Trends at the level of nervous tissue include the pro-inflammatory transformation of microglial cells towards the M1 functional pole, progression of oxidative stress, and functional dysfunction of neurons [128-130]. Most of these data were obtained in experimental studies and human autopsies. Specifically, gene expression profiling was conducted on postmortem prefrontal cortex samples from individuals who did not use psychotropic drugs but with a history of major depressive disorder compared to control samples [131]. Identified were markers of apoptotic and oxidative stress, and increased expression of cytokines: IL-1α, IL-2, IL-3, IL-5, IL-8, IL-9, IL-10, IL-12A, IL-13, IL-15, IL-18, IFNγ, and lymphotoxin-α (TNF family). Many of these cytokines act through receptors that activate nonreceptor tyrosine kinases of the JAK family, whose pathogenetic role in depression is well justified [123].

Negative changes in depression can be exacerbated by nonpsychogenic factors damaging the brain, such as local and systemic brain hypoxia [132], disruptions in the integrity of the blood-brain barrier [133], low-grade systemic inflammation phenomena, including increased intestinal barrier permeability to endotoxins (LPS) and other potentially brain-damaging factors, dysfunction of the immune and cardiovascular systems [133-137]. Thus, the link between depression and morbid obesity, metabolic syndrome, type 2 diabetes, and other clinical phenomena of low-grade inflammation is not surprising [122]. In turn, chronic stress and depression, through neuroendocrine regulation dysfunction, contribute to forming a vicious pathogenetic circle linking these pathologies with low-grade inflammation [138-140].

Thus, chronic stress and depression are pathogenetically linked to pro-inflammatory mechanisms of cellular stress and neuroinflammation. A distinctive feature of neuroinflammation, compared to extreme physiological and borderline manifestations of tissue stress, is the presence of morphofunctional changes in specific brain regions, namely local degenerative changes associated with stress and depression.

4.4. The Significance of Morphological Changes for the Verification of Neuroinflammation in Chronic Stress and Depression

Each typical variant of inflammation presents morphological characteristics. Classic inflammation is characterized by various signs of an inflammation focus; systemic inflammation by morphological signs of microcirculatory disorders and disseminated intravascular coagulation; and local low-grade inflammation by signs of tissue degeneration, lacking classic signs of an inflammation focus or specific morphological phenomena of critical microcirculatory disorders at the systemic level. Neurodegeneration can manifest as atrophy—reduction in tissue volume and neuron count—but also as pseudo-hypertrophy, associated with an increase in the number or size of glial cells, while the number of dysfunctional neurons remains the same or decreases [141, 142].

In depression, some patients may not exhibit significant morphological changes in the brain, while others may show such changes. Evidently, pronounced morphofunctional changes characterize only a specific pathogenetic stage of depression, which can be associated with the presence of low-grade neuroinflammation (Table **2**).

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Table 2. Degenerative Changes in Specific Compartments of Gray and White Matter in the Brain in Depression.

Method	Atrophy	Hypertrophy	References
MRI	Thalamus, precentral gyrus, parahippocampal gyrus, hippocampus	-	[143]
VBM and fractional anisotropy	Corpus callosum, superior corona radiata, cingulate gyrus, superior longitudinal fasciculus	-	[144]
MRI	Left parabelt complex, right perirhinal ectorhinal cortex, right area PHT and right ventral visual complex	Left primary sensory cortex	[145]
MRI1	Right pallidum	Left superior frontal gyrus, lingual and fusiform gyrus	[146]
MRI, VBM2	Cerebellum (GMV)	-	[147]
MRI, VBM	Amygdala, right parahippocampal gyrus	-	[148]
MRI	Left hippocampus	-	[149]
MRI	Dentate gyrus in the hippocampal body	-	[150]
MRI3	Hippocampus	-	[151]
MRI	Midbrain	-	[152]

Note: 1 - Study on postpartum depression, 2 - Study on late-life depression, 3 - Results obtained in depression and bipolar disorder. MRI - Magnetic Resonance Imaging, VBM - Voxel-Based Morphometry, GMV - Gray Matter Volume.

3.5. The Scope of Application of NIIS in Clinical Practice and Experimental Research

Accepting this position integrates the progression of pathologies among individuals who have encountered various stressors early in life, as well as a more severe course of the pathological process among those typically identified as at risk in epidemiological studies: those with metabolic syndrome, obesity, chronic systemic diseases, and infectious pathologies leading to psycho-emotional disorders such as COVID-19—in existing theory. Specifically, the presence of a diathesis could underpin the development of conditions like long COVID (Table **3**). Consequently, the empirical foundation of the NIIS model is supported by conditions that manifest low-grade systemic inflammation, the cumulative effects of acute or chronic stress, and significant changes in mental health.

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Table 3. Integration of Low-Grade Systemic Inflammation, Stress Effects, and Mental Health Alterations in the NIIS Model Across Diverse Pathologies.

Disease/Pathological Condition	Low-grade Systemic Inflammation	Acute Stress/Cumulative Chronic Effects	Mental Changes	References
Major Depressive Disorder	Yes	Yes	Yes	[21, 153-155]
Cardiovascular Diseases	Yes	Yes	Yes	[156-157]
Type 2 Diabetes Mellitus	Yes	Yes	Yes	[155, 158,159]
Alzheimer's Disease	Yes	Yes	Yes	[160-162]
Rheumatoid Arthritis	Yes	Yes	Yes	[163-165]
Irritable Bowel Syndrome (IBS)	Yes	Yes	Yes	[166-167]
Post-Traumatic Stress Disorder (PTSD)	Yes	Yes	Yes	[21,168-171]
Atherosclerosis	Yes	Yes	Yes	[21,120, 172]
Post-COVID syndrome	Yes	Yes	Yes	[173]
Stress, anxiety and depression	Yes	Yes	Yes	[174-177]
Schizophrenia	Yes	Yes	Yes	[178-180]
Osteoarthritis	Yes	Yes	Yes	[181]
Systemic lupus erythematosus	Yes	Yes	Yes	[182]

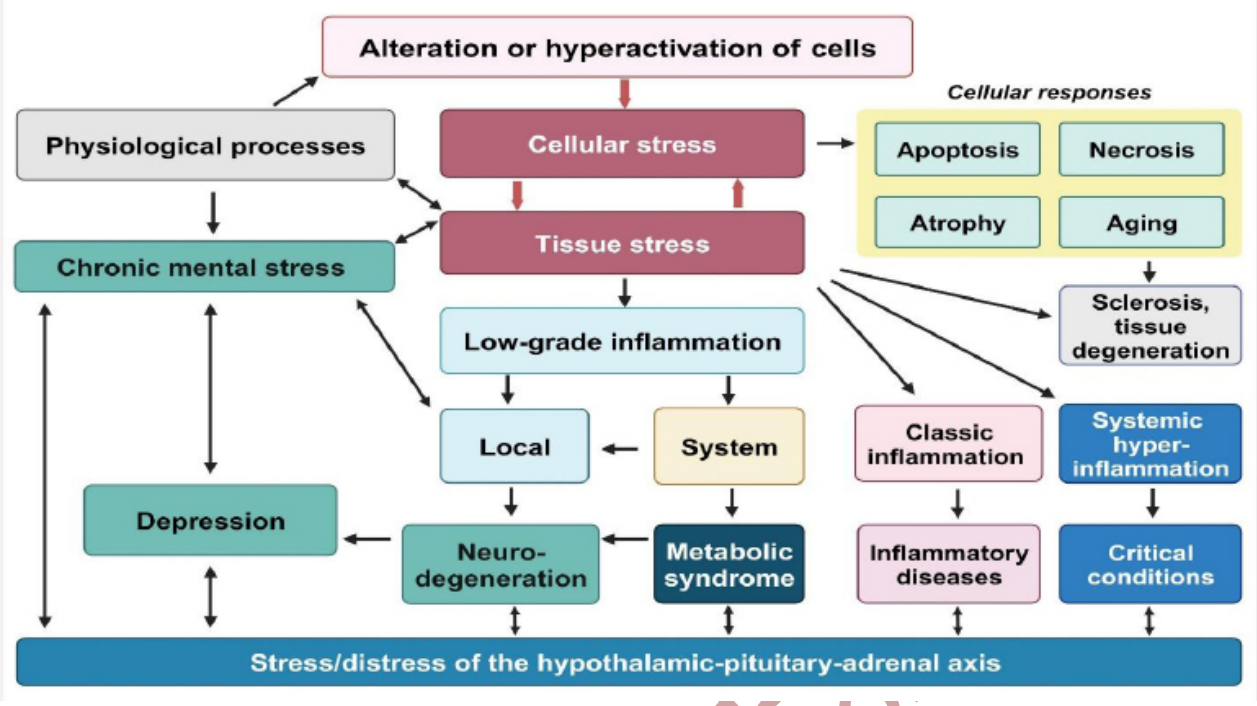

Fig. (5). Inclusion of chronic stress and depression in the system of general pathological processes interconnected by pro-inflammatory mechanisms of tissue stress.

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The NIIS Model also has significant applications in both clinical settings and experimental research. This model elucidates the development of pathologies in individuals or animals subjected to various early life stressors, as well as the more severe progression of pathological processes among individuals identified as at risk in epidemiological studies. This group includes individuals with metabolic syndrome, obesity, chronic systemic diseases, and those affected by infectious pathologies that lead to psychoemotional disorders, such as COVID-19. In such cases, the existence of a diathesis may form the basis for conditions like long COVID, thereby underscoring the relevance of the NIIS model to conditions characterized by low-grade systemic inflammation, the cumulative effects of acute or chronic stress, and notable mental health changes (Table **3**).

Furthermore, adopting the NIIS Model implies that in translational medicine and experimental practices aimed at modeling similar conditions, including PTSD-like states, two-stage models are favored. These models first establish a low-grade systemic inflammation (predisposing individuals to heightened sensitivity to subsequent stressors) before single-stage models that only trigger a stress response [183].

CONCLUSION

The NIIS provides a comprehensive framework for understanding the intricate link between chronic stress and depression. This model elucidates how prolonged cellular pro-inflammatory stress in neurons and microglia leads to neuroinflammatory pathways, resulting in neurotransmitter imbalances, disruptions in neuronal and glial homeostasis, and low-grade neuroinflammation. These processes are critical in the transition from normal stress responses to pathological conditions, contributing significantly to the pathogenesis of depression.

Our investigation highlights several key findings. The NIIS model integrates neuroimmune-inflammatory responses into the conceptual framework of the stress-depression interaction, offering a holistic view of the underlying mechanisms. In particular, neurotransmitters, particularly through their engagement with G-protein-coupled receptors, significantly influence the regulation of cellular stress signaling pathways in healthy states. Chronic psychological stress disrupts this delicate balance, precipitating neuronal excitotoxicity in key brain regions and shifting the physiological pro-inflammatory milieu toward tissue stress and subsequent neuroinflammation. This change is characterized by oxidative stress and a pro-inflammato-

ry phenotype in both neurons and glial cells, leading to widespread cellular dysfunction. Moreover, this neuroinflammatory process often extends beyond its local origins, intertwining with systemic low-grade inflammation, thereby exacerbating the dysfunction of biological barriers and increasing the brain's vulnerability to detrimental factors.

Fig. (**5**) illustrates the inclusion of chronic stress and depression in the system of general pathological processes interconnected by pro-inflammatory mechanisms of tissue stress. This visual representation underscores the interplay between chronic stress, neuroinflammation, and depression, emphasizing the integrative approach of the NIIS model.

The NIIS model advances our understanding of the etiopathogenesis of depression by delineating the specific cellular and molecular pathways involved. This insight is crucial to developing precise therapeutic interventions aimed at mitigating the effects of chronic stress and preventing the onset of depression. Future research should focus on identifying specific molecular targets within neuroimmune-inflammatory pathways to develop novel therapeutic strategies. Furthermore, the identification of biomarkers associated with neuroinflammation and neurotransmitter imbalances could facilitate early diagnosis and intervention in people at risk for depression. Conducting clinical trials to test the efficacy of anti-inflammatory treatments and neurotransmitter modulators in reducing depression symptoms and improving mental health outcomes is also essential. Emphasizing holistic treatment approaches that combine pharmacological interventions with lifestyle modifications, such as stress management techniques and dietary changes, is important to address the multifaceted nature of depression.

In conclusion, the NIIS model provides a robust framework for understanding the complex interplay between chronic stress and depression. By elucidating the molecular and cellular mechanisms involved, this model paves the way for the development of innovative therapeutic interventions aimed at improving mental health and alleviating the global burden of depression.

LIST OF ABBREVIATIONS

AHN = Adult Hippocampal Neurogenesis

ATF4 = Activating Transcription Factor 4

AP-1 = Activator Protein 1

AKT = Protein Kinase B (also known as PKB)

AMPK = AMP-Activated Protein Kinase

ATR = Ataxia Telangiectasia and Rad3 Related

ATM = Ataxia Telangiectasia Mutated

BBB = Blood-Brain Barrier

CNS = Central Nervous System

GABA = γ-Aminobutyric Acid

GPCR = G Protein-Coupled Receptor

GMV = Gray Matter Volume

HIF = Hypoxia-Inducible Factor

HSF = Heat Shock Factor

IL = Interleukin

IFNγ = Interferon Gamma

JAK = Janus Kinase

LPS = Lipopolysaccharide

MAPK = Mitogen-Activated Protein Kinase

mTOR = Mechanistic Target of Rapamycin

MRI = Magnetic Resonance Imaging

NF-κB = Nuclear Factor Kappa B

NMDAR = N-Methyl-D-Aspartate Receptor

NRF2 = Nuclear Factor Erythroid 2-Related Factor 2

PI3K = Phosphoinositide 3-Kinase

PKA = Protein Kinase A

PKC = Protein Kinase C

PKR = Protein Kinase R

PTSD = Post-Traumatic Stress Disorder

STAT = Signal Transducer and Activator of Transcription

UPR = Unfolded Protein Response

VBM = Voxel-Based Morphometry

AUTHORS' CONTRIBUTIONS

All authors contributed to the conception and design of the study. A.S., *e.g.*, and D.H. conceived and drafted the manuscript. M.K., V.C., *e.g.*, A.S., and D.H. discussed the concepts of the manuscript. All authors have read and approved the article.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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