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Anxiety Disorders

The Impact of Translational Research

*Edited by Carlos M. Contreras
and Ana G. Gutiérrez-García*



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IntechOpen Book Series

Nervous System and Mental Health

Volume 6

Aims and Scope of the Series

Mental health is frequently linked to the nervous system. Conversely, disturbances in the nervous system often lead to mental health problems. However, this linkage is not as clear as it is commonly accepted. Mental health is usually described using subjective terms, which are based on psychological and psychiatric symptomatology. Diagnosis of a mental illness is made through the presence of the subjective symptoms characterizing the illness.

On the other hand, the nervous system has been deeply investigated using objective measures, including molecular, genetic, imaging, pharmacological and physiological ones. It is essential to combine objective views of the nervous system with subjective perspectives on mental health to develop an integrative approach to understanding human cognitive functions and achieving overall well-being. In this book series, experts in various fields of the nervous system and mental health will present their views on these challenging topics.

Meet the Series Editor



Dr. Toshikazu Shinba is a psychiatrist and neuroscientist who has been working in both clinical and basic research fields. He has been affiliated with the Tokyo Institute of Psychiatry, Department of Neurophysiology and Stress Disorders Project, and now works as a psychiatrist at Shizuoka Saiseikai General Hospital, Department of Psychiatry. The primary focus of his research is the electrophysiological analysis of attention and arousal in both humans and rodents. In clinical research, EEG, heart rate variability and skin conductance have been measured in mental disorders and arousal/consciousness disturbances. In basic research, single neuronal firing and EEG recordings have been assessed in rats. His research interests cover physiological rhythms related to attention, arousal, and consciousness in both the central and peripheral nervous systems, with a focus on understanding mental states.

Meet the Volume Editors



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Preface

Through natural selection and evolution, organisms have developed critical survival strategies that have evolved over millions of years, beginning with the possession of a nervous system (even in the simple form of a ganglionic nervous system) and culminating in high expression through centralization of the nervous system.

Many organisms that lack an organized nervous system but possess neural networks employ strategies to detect danger, such as jellyfish and other similar species whose primitive systems evolved in a rudimentary way yet sufficiently to detect risks and escape predators.

It is almost impossible to determine at what stage in phylogeny a complex defense mechanism began. It may first be initiated by the capture of environmental information through sensory systems, followed by integration, in which vegetative and motor responses participate in cases of advanced evolutionary nervous system centralization that involve an emotional component. The combination of these responses entails developing strategies to cope with threatening situations. These eliciting responses are, in most cases, learned through prior experience, but in many other cases, they are simply programmed into the genome.

One of these emotions that is elicited by threatening situations is anxiety. Viewed from the above perspective, anxiety is a highly adaptive process that allows individuals to cope with threatening situations through learned behaviors or pre-programmed processes. Similar to a reflex arc, anxiety can enable the establishment of effective coping strategies. The result is protection of an organism through immediate vegetative and motor responses that lead to the release of stress hormones (e.g., adrenaline and cortisol). These substances then prepare the organism for a fight-or-flight response, thereby ensuring its safety.

Under abnormal circumstances, however, when a real threat ends and no longer presents a real danger, the expression of anxiety is no longer necessary for survival. In this case, the body's response to nonexistent threats persists, and high levels of stress hormones remain elevated, impairing the individual's functioning and affecting health.

Here, the reaction designed and implemented by evolution and natural selection as a protective response turns against the individual when it loses its fundamental role: survival. This is the case with pathological anxiety; it is no longer a defensive process.

All known species are under constant strain. Geopolitics has changed at an unimaginable pace in the past centuries. Climate change poses a global threat to all species, including plants, potentially impacting future food resources. The threatened habitats of animal species also merit mention. Of course, all of this has repercussions for the human species. Anxiety in its pathological form is often

common in any country, at any age, with any gender, and so on. Stress is constant and increasing every day, and the development of anxiety is consequently becoming more common. It is no longer an adaptive response, and its pathological form affects all levels of life, including family, education, and employment.

The high prevalence and incidence of anxiety require extensive studies of its pathophysiology and the development of effective treatments with less addictive potential than those that are currently available.

Undoubtedly, the best species for studying anxiety is *Homo sapiens*, but this entails clear experimental and ethical limitations. This is where animal models become important. For example, in animal models, researchers can observe movements and changes in hormone, neurotransmitter, and other substance secretion, allowing extrapolations to the function of the human organism and its potential applications to emotional and mental health.

This underscores the importance of translational research, which is becoming increasingly vital. The path from discovery in laboratory animals to application in humans is long and complex, but it must start somewhere.

This book begins with considerations of the pathophysiology of anxiety, continues with clinical observations of anxiety, presents proposals to control its pathological progression, and concludes with models to address other therapeutic models of anxiety.

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Chapter 1

Relationship Between Anxiety, Stress, Resilience and Brain Plasticity

Ana G. Gutiérrez-García and Carlos M. Contreras

Abstract

Resilience and vulnerability do not necessarily represent opposite processes. Resilience is the capability to recover from adversity, while vulnerability is a tendency toward developing a maladaptive response to threatening situations. Both processes share forebrain structures and their connections with subcortical structures. The proper functioning of these structures and connections leads to the successful selection of strategies to cope with adverse situations, resulting in a useful adaptive form of anxiety. Brain structures involved in both processes include the prefrontal cortex, anterior cingulate, and insula, as well as the amygdala, hippocampus, nucleus accumbens, and ventral tegmental area, among others. Both processes are based on the plasticity of neuronal tissue, which arises from interactions between neurons, glial elements, neurotrophic factors, and an adequate balance of glutamate/ γ -aminobutyric acid activity. Interactions among these factors give rise to the elimination of useless strategies or the acquisition of new strategies that allow recovery from the previous state or even a step forward in acquiring new strategies to face different environmental threats. This chapter reviews the ways in which the brain can develop adaptive anxiety and, consequently, resilience, but also vulnerability and, consequently, the development of anxiety disorders.

Keywords: resilience, stress, adaptive anxiety, pathological anxiety, brain plasticity

1. Introduction

Anxiety is an adaptive response, a natural emotion that arises to cope with danger and plays a fundamental role in survival [1]. Maladaptive anxiety is a pathological condition. In this case, all corporal and emotional reactions remain, but the threatening stimuli are no longer present due to alterations in brain circuits that mediate the response to threats, with a considerable impact on reward systems and brain systems that mediate cognitive control and social processes [2]. This is the case in pathological anxiety, through dysfunction of the limbic system, its connections, and the hypothalamic–pituitary–adrenal (HPA) axis, as well as genetic factors [3].

Anxiety is closely related to, and inseparable from, stress. Stress refers to the body's response to a stressful situation that produces a functional response. The

concept of resilience, as accepted by the National Institutes of Health, considers that the response to a stressful situation and the possibility of developing anxiety can be modified based on experience, learning, and the environmental setting [4], which allows adaptation to trauma, adversity, tragedy, and even significant and ongoing stressors. Thus, resilience allows the organism to maintain or recover its original functional state [5] and can be considered an adaptive response to adversity [6].

Different biological systems have some degree of resilience. Even some ecosystems exhibit a considerable degree of resilience [7]. Everything in nature generally tends to recover its original form after a catastrophic event. In behaving species, resilience is based on the ability to utilize cognitive, emotional, and physiological resources in response to a stressor and on the conservation or enrichment of these resources once the stressful event has been eliminated [8]. In species with evolved neural tissue, the response to a stressful situation leads to a beneficial and highly adaptive form of anxiety. Therefore, resilience to chronic stress is an active process that involves much more than simply avoiding the harmful effects of long-term stress.

Allostasis refers to the capability of achieving stability. It is an active process by which the body responds to daily events and maintains homeostasis. In the case of excessive stress, allostasis is not deactivated and remains when it is no longer needed; it then progresses to allostatic load [9], with the protective participation of stress hormones [10]. In adaptive anxiety, there is a correct response to stress. Conversely, in a maladaptive response to stress, allostatic overload can occur, leading to pathological anxiety and vulnerability. Thus, treatments for anxiety disorders, in addition to being aimed at reversing the damaging effects of stress and allostatic overload, also generate resilience in individuals who are inherently more vulnerable to pathological anxiety [11].

2. Anxiety, resilience, and epigenetics

Anxiety, although a normal response to stress, can become a difficult and persistent problem that disrupts daily life [12]. Genetic factors and environmental aspects, including social support, parental care, and healthy habits (e.g., physical exercise), contribute to individual differences in strategies to cope with adversity. Conversely, exposure to repetitive stressors and a lack of social support contribute to the generation of allostatic overload, resulting in maladaptive anxiety and health disorders that involve cognitive, endocrine, immunological, and other alterations, eliciting metabolic, cardiovascular, neuroendocrine, autonomic, immune, cognitive, and emotional disorders [13], such as pathological anxiety.

The concept of epigenetics has generated much debate, and experiments have been performed to quantitatively characterize this phenomenon [14]. C.H. Waddington coined the term “epigenetic” in an attempt to explain the complex and dynamic interactions between the environment during development and the genome that may lead to phenotypic modifications [15]. Epigenetic influences do not modify DNA sequences but can modulate gene expression through histone acetylation, which produces greater transcriptional activity, whereas the reverse process (i.e., histone deacetylation) tends to repress transcription, influencing the plasticity of developing neuronal circuits [16]. The effects of chronic and unmanageable social and psychological stress in humans, especially during the first years of life, can cause

shorter telomeres, which have been associated with a higher risk of developing behavioral disorders [17, 18] as a consequence of exposure to stressors during critical periods of development [19]. Thus, environmental experiences can produce long-term changes in neuronal function and, consequently, behavior [20]. Additionally, to counteract these alterations, an inverse process may be considered that involves pro-resilience factors, including the histone acetyltransferase/histone deacetylase ratio, the dehydroepiandrosterone/cortisol ratio, testosterone levels, and neuropeptide Y [21].

Epigenetics is of interest in such disorders as anxiety and depression because epigenetic changes are a means of explaining how life events, such as stress, may cause persistent changes in the brain and behavior. Epigenetics also offers a potential explanation for how individuals who have genetic similarities can present large differences in susceptibility and resilience to disease, illustrating how stressors and the environment alter gene expression through multiple mechanisms that may predict susceptibility to psychiatric illness in adults [22]. Epigenetic imprints that underlie the plasticity of brain cells and circuits contribute to the persistent impact of life experiences on an individual's behavior and physiology, from the formation of long-term memory to the after-effects of traumatic events [23]. Plasticity that is associated with epigenetics can be useful in situations that require resilience, without producing permanent genetic changes that, in turn, could have certain disadvantages, such as an inability to develop new adaptation processes [24].

3. Resilience to anxiety and development

Early childhood stress refers to a range of adverse childhood experiences, such as the loss of a parent, emotional, physical, or sexual abuse, neglect, or exposure to violence, which impact critical periods of neurodevelopment [25]. Childhood stress can have effects on brain plasticity that modify the stress response, immune signaling, and emotional regulation, all of which increase vulnerability to psychiatric disorders, such as anxiety and depression [26, 27]. In animal models, early life stress reduces hippocampal volume, sensitizes the amygdala, and affects the development of the medial prefrontal cortex (mPFC). These changes generally follow neuroinflammatory processes, leading to failure in emotional regulation and exaggerated fear and anxiety responses [28]. Conversely, during exposure to early life stress, social interactions increase plasticity in prelimbic and infralimbic mPFC cortices, illustrating the basic role of these structures in the process of coping with adversity [29].

After experiencing childhood trauma, high and long-lasting levels of anxiety, in parallel with high activity of the HPA axis and consequently high levels of cortisol secretion, can occur [30]. Prenatal stress and childhood trauma have been linked to an overactive HPA axis that progresses to chronic hypercortisolemia in adulthood [31]. However, this is debatable because some individuals develop greater resilience to the negative effects of uncontrollable stressors after being exposed to harmful experiences during childhood [32], with the participation of several neurotransmitter systems and molecular processes that lead to changes in neuroplasticity [33]. The fact that not all humans who are exposed early to uncontrollable traumatic experiences develop emotional disorders implies important individual differences in the ability to cope with environmental situations; that is, some individuals are resilient, and others are not. Many individuals do not develop allostatic overload; instead, adaptive anxiety appears,

a process that is more common than extraordinary. These individuals tend to emerge healthy and successful despite living in high-risk environments. They are also able to overcome the harmful effects of adversity and recover from traumatic experiences. Thus, the brain responds to experiences with structural and functional plasticity, and hormones play a crucial role, along with neurotransmitters and other mediators in a complex network.

4. Neurobiology

Certain environmental factors can produce significant behavioral and morphological changes in a process that involves behavioral and even morphological plasticity, leading to an adaptive response. This epigenetic process (see above) influences the function of brain structures that regulate anxiety and their connections to the HPA axis [34]. Epigenetic mechanisms regulate synaptic plasticity in various ways, such as in memory [35]. Resilience may involve the extinction of fear memories [36] through the actions of neurotrophic factors on hippocampal neurogenesis [37, 38].

During stress, the HPA axis, the autonomic nervous system, metabolic systems, and the immune system are activated, preparing the organism to escape a predator or other environmental threat [39]. Meanwhile, the amygdala complex is responsible for regulating the response when the stress situation is prolonged [40, 41]. This ultimately leads to the sustained release of glucocorticoids and an autonomic response that includes overactivation of the autonomic system, with the subsequent release of epinephrine and norepinephrine. When this vegetative response persists over time and is disproportionate to a real and acute response or threat, it will lead to allostatic overload, which contributes to greater vulnerability to stressors [42] and the consequent appearance of pathological anxiety.

In rodents, the process of neuronal plasticity involves the formation of new synaptic connections and new neurons, referred to as neurogenesis. This clearly occurs in the dentate gyrus of the hippocampus and in the subventricular zone of the lateral ventricle [43]. Some studies found that hippocampal neurogenesis promoted resilience to stress in mice subjected to chronic social defeat [44], but some reports contradict this assumption [45]. The constant presence of higher plasma levels of glucocorticoids, particularly cortisol, can inhibit neurogenesis in the hippocampus, which can be significantly reversed by antidepressant drug administration [46, 47]. Antidepressant treatments with anxiolytic actions restored synaptic function that was altered and led to the disease state [48].

Among other neurotransmitters, dopamine is involved in anxiety [49]. Mice that are susceptible to stress exhibit higher dopaminergic neuron activation in the ventral tegmental area (VTA) connection to the nucleus accumbens and lower activity in VTA connections to the mPFC [50]. These differences did not occur in stress-resilient mice, whose activation levels of these circuits were similar to those of control mice that were not subjected to the stress situation [51, 52]. The nucleus accumbens receives dopaminergic projections from the VTA and glutamatergic projections from the hippocampus, PFC, amygdala, and thalamus. γ -Aminobutyric acid (GABA)ergic neurons contain dopamine receptors, and this complex circuit is related to reward-directed behaviors [53, 54]. Certain glutamatergic afferents act in both reward and aversion [55–58], suggesting that

there are alterations in glutamatergic function in the nucleus accumbens in pathological anxiety [59]. Mice that underwent voluntary physical exercise developed resilience to chronic stress, in parallel with GABAergic hippocampal neuron activation, but neural activity decreased in the mPFC with the participation of the nucleus reuniens [60].

The well-known sexually dimorphic presence of anxiety may be related to different regions that participate in resilience processes. For example, the activation of somatostatin interneurons in the prelimbic cortex in male mice resulted in resilience to stress, indicating the participation of GABAergic microcircuits in this process. However, these changes were observed in the ventral hippocampus in female mice [61, 62]. In female resilient mice, allopregnanolone plays a fundamental role through its actions on GABA_A receptors in the prelimbic region of the mPFC and basolateral amygdala [63]. However, when the anxiety disorder has already been established, neuronal alterations in these circuits can be exacerbated, preventing learning and perpetuating anxiety disorders. In male rodents, the proper regulation of glutamate, GABA, epinephrine, norepinephrine, serotonin, and dopamine function in the amygdala, hippocampus, and PFC influences the management of threatening situations [64], impinging on anxiety regulation with the participation of the medial amygdala during the process of anxiety produced by chronic stress exposure [65].

Excess glucocorticoid secretion in stressful situations produces changes in neurotrophic factors that may affect microglial morphology and function [66]. Excitatory glutamatergic pyramidal neurons and inhibitory GABA interneurons, referred to as an excitation/inhibition (E/I) functional model in the mPFC, are useful for understanding the actions of some psychotropic drugs with anxiolytic effects [67]. Dexamethasone, in the long-term, produces depression-like behavior in animal models and a reduction of GABAergic interneurons in the mPFC, leading to an imbalance in the E/I process [68].

In mice, chronic noise exposure produces microglia-mediated synaptic phagocytosis of inhibitory synapses in the lateral amygdala, thereby affecting the E/I balance and producing anxiety-like behavior [69]. An adequate balance between GABA and glutamate activity may regulate resilience or vulnerability to anxiety produced by a stressful, threatening situation [70]. Relevant to this process is the participation of the metabotropic glutamate family of G protein-coupled receptors in the mPFC, basolateral amygdala, nucleus accumbens, and ventral hippocampus through their involvement in susceptibility to stress-induced anhedonia and resilience to stress-induced anxiety-like behavior [71]. Therefore, correct interactions among neurotrophic factors, glial activity, and glutamate/GABA E/I balance may explain the processes involved in adaptively useful anxiety. Conversely, an imbalance may explain the presence of pathological anxiety.

The presence of amygdala nuclei is shared by multiple species. The amygdala complex is a brain region that is involved in the regulation, acquisition, storage, and expression of fear [72, 73], including reciprocal connections with the mPFC [74] and other structures, such as the hippocampus [75]. These anatomical features may be related to the amygdala's role in regulating emotions and cognition in reptiles, birds, and mammals, suggesting similar processes across species to cope with stress.

Before a resilience or vulnerability response occurs, any aversive situation involves a certain degree of fear and anxiety. Sensory systems detect environmental changes, and this information undergoes complex processing by cortical and

subcortical nuclei, at least in vertebrates. In humans, the ventromedial PFC regulates adaptations to stress [76]. Emotion-regulating limbic circuits in the forebrain react to both appetitive and aversive environmental cues, triggering approach-avoidance and defensive motor responses. Amygdala activity increases in response to both pleasurable and unpleasant contexts. Other structures of the mesostriatal system are involved in reward processing. The nucleus accumbens and ventromedial PFC are selectively activated by pleasurable stimuli [77]. In highly resilient individuals, aversive stimulation reduces activation of the anterior cingulate cortex and insula, while attenuating activity in the ventromedial PFC. Individuals with low resilience exhibit greater activation of the anterior insula [78], with the influence of interhemispheric cortical predominance in some cases [79].

Imaging studies have shown that forebrain structures, such as the human PFC and its connections to limbic regions, ventral striatum, and thalamic subcortical structures, are involved in emotional processes [80]. Activation of the anterior cingulate cortex is related to lower social anxiety and better emotional regulation skills, likely through the inhibition of amygdala activation. In non-anxious subjects who are subjected to fear anticipation tasks, the insula, rostral anterior cingulate cortex, and dorsolateral PFC are deactivated compared with anxious subjects [81]. Low basal amygdala activity corresponds to high levels of resilience [82]. In patients with posttraumatic stress disorder and subjects who are exposed to a traumatic experience, a decrease in prefrontal cortical functional connectivity with the amygdala was observed [83]. Meanwhile, high amygdala activity may be helpful after traumatic experiences [84], meaning that both adaptive and pathological anxiety share the same neuronal circuit, which is modified depending on whether the brain tends toward resilience and thus toward adaptation or vulnerability.

5. Neurotrophic factors, anxiety, and resilience

The expression of resilience represents an active process that is based on molecular, hormonal, and neuronal responses that involve neurotransmitter systems, the HPA axis, and neurotrophic factors (e.g., brain-derived neurotrophic factor [BDNF]), among others [85]. Resilience appears to be a consequence of the action of neurotrophic factors that influence brain circuits involved in emotional regulation, such as the hippocampus, mPFC, nucleus accumbens, VTA, lateral habenula, amygdala, and bed nucleus of the stria terminalis, with the essential participation of BDNF [86]. BDNF is primarily responsible for neuronal plasticity and is detectable in several species other than mammals, including some fish species [87], which represents the possibility of an early evolutionary signal of neuronal plasticity.

Neurotrophic factors may influence the restoration of damaged neurons [88] and exert actions on the density of dendritic spines and synaptic function, which influence behavior [89]. Brain BDNF content changes as alterations in behavior occur [90]. In a rodent study, chronic defeat stress produced the long-lasting downregulation of BDNF transcripts and increased histone methylation, effects that were reversed by a tricyclic antidepressant [91]. Consistent with this finding, the administration of antipsychotics [92], antidepressants [93], and anxiolytics [94] modified BDNF levels in the brain. Therefore, clinical recovery from psychiatric illnesses reflects brain plasticity processes.

Neuronal participation in all of these processes is not limited to neurons and synapses. Glia also participates in synaptic plasticity [95]. Chronic stress activates and promotes the proliferation of microglia and macrophage infiltration in the mPFC, increasing its neuronal activation and leading to changes when confronting a threatening situation [96]. The inactivation of glial cells may prevent some consequences of chronic stress, such as anhedonia, which is associated with chronic unpredictable stress in rodents [97]. Functional relationships between glia and neurons drive neuronal plasticity, whose regulation by trophic factors is widely represented in the animal kingdom [98]. In the presence of agents that are harmful to neurons, glial cells are able to alter their morphology [99]. For example, inflammatory cytokines mobilize microglia [100], and the actions of these cells can drive the formation of new synapses or exert a pruning effect on damaged synapses [101].

Astrocytes are cells that are able to regulate synaptic activity [102] and neuronal connectivity through their actions on the formation or pruning of synapses, which are the basis of plasticity [103]. Across animal species, neurogenesis and neuronal plasticity are determining factors that influence strategies to cope with stressful situations, underscoring the participation of glial cells in the process of adaptive or maladaptive anxiety. Neurotrophic factors, glia, and microglia exert fundamental actions on the regulation of dendritic spines. The functional role of dendritic spines is relevant in learning processes [104–106]. Adaptive anxiety allows the acquisition of new strategies and the conservation of old successful strategies, while promoting the forgetting of useless strategies to cope with adversity, thus achieving anxiety in its adaptive form.

6. Conclusion

The neocortex, its connections, neurotrophic factors, glial activity, and glutamate/GABA balance comprise circuits and neurochemical interactions that are related to adaptive anxiety. Imbalances in these systems appear to be related to pathological anxiety. Evolutionary differences that reflect distinct environmental settings are a useful characteristic for any species. The fight-or-flight response allows the individual to survive. In species that develop some type of neocortex and its connections, if the strategy for coping with adverse situations is successful, then there is a high likelihood of repeating that strategy, indicating a useful learning process and the consequent acquisition of an adaptive anxious state. Direct and indirect connections of sensory systems with the emotional brain determine the formation of strategies that, if successful, strengthen resilience; otherwise, they lead to greater vulnerability to developing anxiety as a morbid process.

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Conflict of Interest

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Chapter 2

Early-Life Stress and Psychiatric-Like Behaviors in Rodents: Reconsidering Sensitive Periods

Yuki Kajita

Abstract

Early-life stress paradigms in rodents, including maternal separation, are widely used to model the influence of adverse early experiences on emotional and psychiatric behaviors later in life. Early research in this field has largely focused on the stress hyporesponsive period (SHRP), an early postnatal stage characterized by attenuated hormonal stress responses, suggesting that early postnatal development represents a uniquely regulated phase of stress sensitivity. However, growing evidence indicates that stress vulnerability in rodents is not restricted to the SHRP. Stress exposure at different postnatal stages produces long-lasting changes in anxiety- and depression-like behaviors, as well as alterations in neural structure and circuit function. Importantly, these effects depend on the timing of stress relative to ongoing brain maturation, rather than reflecting uniform changes in baseline stress hormone activity. Studies using maternal separation or early weaning at defined developmental stages further support the existence of multiple sensitive periods, during which distinct neural circuits show stage-specific susceptibility to environmental perturbations. Together, these findings suggest a reconsideration of sensitive periods in rodent early-life stress models and provide a developmental stage framework for interpreting the variability across experimental designs and behavioral outcomes.

Keywords: early-life stress, maternal separation, rodent model, postnatal development, stress hyporesponsive period, sensitive period, neural circuit plasticity, anxiety-like behavior, depression-like behavior

1. Introduction

Early-life stress is widely recognized as a major determinant of emotional and psychiatric-like outcomes. However, the timing during development when the brain is most vulnerable to adverse experiences remains a central and unresolved issue. Rodent models have been particularly useful in addressing

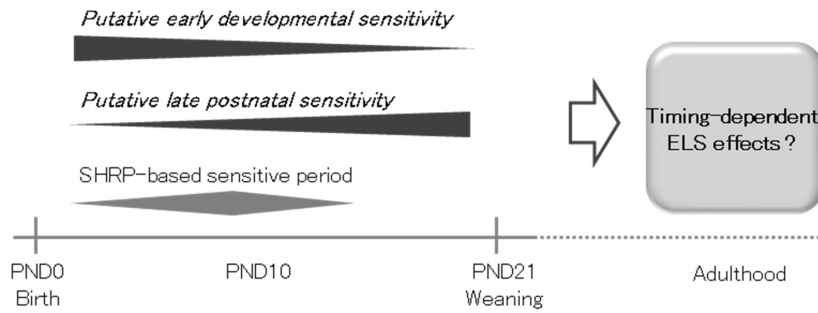


Figure 1.
Schematic illustration of partially overlapping sensitive periods.

this issue, as they allow experimental access to developmental timing, which is difficult to achieve in humans.

Historically, many rodent studies have focused on the stress hyporesponsive period (SHRP), an early postnatal phase characterized by attenuated responses of the hypothalamic–pituitary–adrenal (HPA) axis to stress. This framework strongly influences the conceptualization of early-life stress, often leading to the implicit assumption that vulnerability is either concentrated within or meaningfully defined by this endocrine window.

However, accumulating evidence has complicated this hypothesis. Stress exposure during SHRP can induce lasting neural and behavioral alterations despite blunted peripheral glucocorticoid responses, indicating that neural sensitivity does not necessarily track endocrine output. Concomitantly, stress applied outside the SHRP during later postnatal stages, marked by region-specific synaptic maturation and circuit refinement, produces persistent and sometimes distinct phenotypes. These findings suggest that developmental vulnerability cannot be captured in a single critical period (**Figure 1**).

Early-life stress paradigms limited to postnatal manipulations (e.g., maternal separation) may exert timing-dependent effects through distinct developmental processes. ELS: early-life stress; PND: postnatal day; SHRP: stress hyporesponsive period.

In this review, we synthesize evidence from human and animal studies to reframe early-life stress in terms of multiple sensitive periods defined by ongoing neurodevelopmental processes. We first summarize human data supporting the timing-dependent effects of early adversity and then outline the classical SHRP framework and its biological features. Next, we examine stress sensitivity beyond the SHRP, focusing on the differential effects of maternal separation and early weaning at defined stages on neural circuits and behavior. Finally, we integrate these findings into a developmental stage perspective to help explain the variability across experimental paradigms and species.

2. Human evidence for timing-dependent effects of early-life stress

Exposure to chronic or severe stress during early childhood has been associated with a higher risk of depression, anxiety, and related psychiatric disorders later in

life [1–6]. Epidemiological studies have indicated that this association depends on the age at which stress is experienced, with exposure occurring before approximately 9–12 years of age showing stronger links to later vulnerability than stress encountered at older ages [7, 8].

Brain development begins during the fetal period and extends after birth. During this period, neural circuits are shaped by processes such as cell proliferation, migration, differentiation, synaptogenesis, and synaptic pruning [9–13]. These processes are not evenly distributed across development. Periods of rapid remodeling coincide with increased plasticity and greater sensitivity to environmental influences [14, 15]. Human imaging studies have reported differences in brain structures associated with early stress exposure, particularly in regions involved in emotion and cognition, including the hippocampus, amygdala, and medial prefrontal cortex [16, 17]. The strength of these associations varies with exposure timing.

The mechanisms by which early stress leads to these differences remain unclear. One mechanism that has received attention is the altered regulation of the HPA axis [18–21]. Elevated glucocorticoid levels during development have been linked to structural changes in stress-related brain regions, most consistently in the hippocampus [22–25].

Overall, the available evidence points to the role of developmental timing in shaping the neural effects of early-life stress. Addressing causality and separating timing effects from later-life influences require experimental animal models.

3. Translational insights using animal models

Evidence from human studies suggesting heightened vulnerability during early development has been reinforced by research in nonhuman primates, where experimental conditions can be tightly controlled. Classic experiments initiated by Harlow showed that prolonged social isolation during infancy results in marked and persistent alterations in emotional, social, and exploratory behaviors. Importantly, recovery was limited and appeared to depend on resocialization occurring within an early sensitive period [26, 27]. These studies support the notion that caregiver contact deprivation during development can have lasting consequences, closely paralleling observations in children exposed to severe institutional rearing.

In rodents, early-life stress has most commonly been modeled using maternal separation, in which contact between the dam and pups is interrupted for a defined period. This approach has been explored within the same developmental framework as other manipulations of the early caregiving environment, including early weaning and limited bedding and nesting models [28, 29]. In practice, maternal separation protocols differ substantially across studies, ranging from short repeated daily separations to separations lasting several hours, with the specific design shaped by the experimental questions being addressed [30]. Many studies employed separations of approximately 3 h per day to reduce secondary influences, such as nutritional deficits or hypothermia. Under these conditions, maternal separation reliably induced physiological stress responses in pups and was associated with long-term alterations in HPA axis regulation and neural plasticity, which are thought to contribute to enduring emotional and behavioral phenotypes [31–33].

4. Characteristics of the stress hyporesponsive period (SHRP)

Classical rodent studies have identified the stress SHRP, spanning approximately postnatal days (PND) 4–14 in rats (PND1–12 in mice), as a developmental window during which stress exposure has enduring effects on adult behavior. From the pioneering maternal separation studies by Levine [34] to later neuroendocrine analyses by Plotsky and Meaney [35], SHRP-focused maternal separation paradigms have become a central framework in early-life stress research.

SHRP is characterized by markedly attenuated acute HPA axis responsiveness, reflected by low basal levels of adrenocorticotrophic hormone and corticosterone (CORT; cortisol in humans), and minimal hormonal responses to external stressors [36, 37]. Importantly, prolonged or repeated stress during this period can override this hyporesponsive state, resulting in elevated steady-state CORT levels later in life [30, 38].

Sustained elevations in CORT exert long-lasting effects via mineralocorticoid and glucocorticoid receptors (GRs) [39], influencing dendritic architecture [40], neurotrophic factor expression, and inflammatory cytokine profiles [41]. In parallel, variations in maternal care modulate DNA methylation of hippocampal GR promoters, leading to persistent alterations in GR expression and HPA axis reactivity [42].

GR activation during the SHRP also engages intracellular signaling cascades, including MAPK and CaMKII, which regulate synaptic plasticity and long-term potentiation [43, 44]. These molecular changes provide a mechanistic basis for stress-induced modifications in developing neural circuits and are thought to contribute to long-term vulnerability to psychiatric-like behaviors [45, 46].

Beyond neuroendocrine signaling, maternal separation during the SHRP affects oxidative stress, neurotransmission, myelination, and the gut–brain axis, all of which play important roles in circuit maturation and behavioral outcomes [47–50]. These processes regulate activity-dependent BDNF expression, NMDA receptor subunit composition, and the developmental shift of GABAergic signaling from excitatory to inhibitory, thereby supporting synaptogenesis, circuit assembly, and network synchrony [51–53]. Maternal separation also perturbs multiple neuromodulatory systems, including glutamatergic, GABAergic, dopaminergic, noradrenergic, serotonergic, autonomic, and oxytocinergic pathways, which are essential for coordinated circuit development [54–57]. Recent studies have further indicated that SHRP stress alters microglial activity, producing secondary effects on neurodevelopment [58–60].

Taken together, these findings indicate that early-life stress during the SHRP induces long-term alterations in neural circuit formation through the combined action of neuroendocrine-, molecular-, and immune-related mechanisms.

5. Rethinking the SHRP

Multiple brain regions implicated in depression- and anxiety-like behaviors, including the hippocampus, amygdala, nucleus accumbens, and septal nuclei, are affected by maternal separation [61–63]. Importantly, these regions do not mature simultaneously, suggesting that the timing of stress exposure preferentially affects specific neural circuits rather than producing uniform effects across the brain.

Nevertheless, most maternal separation studies have focused on SHRP or treated the entire preweaning period as a single developmental stage [64], despite earlier suggestions that stress effects may extend beyond SHRP [65].

In rodents, hippocampal maturation, including synaptogenesis and the establishment of stable connectivity, continues until approximately PND30 [66]. Lee et al. proposed that stress-induced hippocampal alterations may occur after PND14. Supporting this idea, early weaning at PND14, involving permanent separation from the dam rather than daily maternal separation, reduced cell proliferation, increased apoptosis in the granule cell layer, disrupted hippocampal development, altered serotonergic gene expression, and induced astrocyte proliferation in the prefrontal cortex [67, 68]. These neurodevelopmental changes were accompanied by hyperactivity and reduced anxiety-like behaviors, resembling ADHD-like phenotypes in rodent models.

Stress exposure outside the SHRP through early weaning also produces sustained HPA axis activation, together with molecular and structural alterations. Circulating corticosterone levels increased immediately after weaning and remained elevated for more than 48 h, in contrast to the transient endocrine responses typically observed following maternal separation during SHRP [69]. This prolonged response was associated with a biphasic pattern of hippocampal glucocorticoid receptor expression, with a transient increase at PND21, followed by a reduction at PND56 in early-weaned male mice, resulting in impaired negative feedback and prolonged corticosterone secretion [70]. These findings suggest that late postnatal stress alters glucocorticoid feedback regulation rather than simply elevating hormone levels.

In addition, early weaning reduced hippocampal BDNF expression and suppressed dentate gyrus neurogenesis, resulting in hyperactivity and anxiety-like behaviors [69, 71]. Structural effects were also evident in the amygdala and prefrontal cortex. The basolateral amygdala showed early accumulation of galactosylceramide and increased myelination, whereas changes in the prefrontal cortex and hippocampus were modest [72]. Together, these region-specific alterations indicated that late postnatal stress preferentially affects circuits involved in emotional processing and behavioral regulation, potentially disrupting the maturation of emotion-regulating networks [71, 73].

Collectively, these studies indicate that stress exposure outside the SHRP engages mechanisms that are partially distinct from those operating during the SHRP, highlighting the characteristic patterns of endocrine and neural vulnerabilities during later postnatal development.

6. SHRP-independent maternal separation

Nakamura et al. examined the effects of early-life stress on the lateral habenula at different developmental stages. They found that maternal separation during PND10–20 preferentially led to anxiety- and depression-like behaviors in adulthood, along with a reduction in the number of GABAergic neurons and hyperactivation of the lateral habenula [74]. In contrast, maternal separation before PND10 did not produce similar changes, suggesting that specific neural circuits are especially vulnerable during discrete postnatal windows beyond the classical SHRP.

In our recent study, we divided littermate male rats into PND1–9 and PND1–20 maternal separation groups. At 8 weeks, we measured depression- and anxiety-like behaviors, plasma corticosterone levels, and dendritic spine density in the ventral hippocampus [75]. Notably, behavioral abnormalities and reduced spine density were only observed in the PND10–20 maternal separation group, whereas the PND1–9 maternal separation group appeared unaffected. Interestingly, plasma corticosterone levels remained similar in both groups, indicating that these neural and behavioral changes can occur without overt HPA axis dysregulation.

These findings align with those of a previous study that compared repeated versus single maternal separation across postnatal stages and showed that stress-induced activation of central circuits, measured by c-Fos, adapted in a developmental-stage-dependent manner, whereas peripheral corticosterone responses remained largely unchanged [76]. This dissociation suggests that the long-term behavioral effects of maternal separation arise from circuit-level adaptations rather than systemic endocrine changes alone.

Overall, accumulating evidence supports the concept of developmental-stage-dependent circuit vulnerability and highlights the limitations of HPA-axis-centered frameworks in explaining the full range of maternal separation-induced neural and behavioral effects.

7. Multiple sensitive periods to early-life stress

The sensitive period of early-life stress cannot be adequately explained by a single critical period, such as the SHRP defined in rodents. Rather, it is better viewed as a process shaped by multiple sensitive periods that differ across brain regions and partially overlap in time [64, 65]. From this perspective, frameworks that focus exclusively on SHRP are likely to miss important aspects of the influence of neural development by early-life stress.

In rodents, PND1–9 is characterized by rapid dendritic spine formation and the initial establishment of neural circuitry. The SHRP (PND4–14) overlaps with this phase and is typically associated with reduced HPA axis reactivity. During the subsequent PND10–30 period, synaptogenesis becomes more pronounced, followed by circuit refinement and the emergence of functional networks [77]. Considering these stages in relation to human development, early postnatal rodent stages roughly correspond to late gestation and the immediate postnatal period in humans (23–32 weeks old), the SHRP overlaps with the neonatal stage (36–40 weeks old), and later postnatal phases parallel infancy through early toddlerhood (2–3 years old). Thus, similar stress exposures may have different consequences depending on the developmental stage at which they occur.

An appreciation of the stage-dependent mechanisms is also relevant when considering intervention strategies. Approaches such as increasing caregiver–infant contact, environmental enrichment, activity-dependent stimulation, or modulation of the gut microbiome using probiotics have been explored. However, their effects are not uniform and appear to vary with developmental stage, sex, and the neural circuits involved [78–81]. Interventions administered earlier in development may preferentially support circuit formation, whereas those introduced later may act more strongly on synaptic adjustment and plasticity. Reports on sex differences in

vulnerability have further suggested that both the timing and responsiveness to interventions may differ between males and females. In addition, heterogeneity in intervention outcomes and stress-related vulnerability may be influenced by species differences, variability in maternal separation paradigms, and differences in rearing conditions. For example, the timing of neuronal maturation is known to differ between mice and rats [82]. Moreover, in maternal separation paradigms, factors such as the duration of separation [83] and the presence or absence of littermates during separation [84] can differentially affect hormonal and behavioral responses. Differences in standard rearing conditions, including housing density and light–dark cycles, may also modulate the effectiveness of interventions. These factors should, therefore, be carefully considered when interpreting results and in the design of future studies.

8. Conclusion

This review highlighted that the long-term consequences of maternal separation cannot be adequately understood within a framework that focuses solely on SHRP. Accumulating evidence has indicated that vulnerability to early-life stress is shaped by the developmental stage, with multiple sensitive windows during which stress exposure can exert lasting effects on brain function and behavior. Importantly, these outcomes were not consistently associated with persistent alterations in basal HPA axis activity, suggesting that developmental timing and ongoing neural maturation may independently contribute to the long-term effects. Viewing maternal separation through a developmental stage-based lens helps reconcile the variability across rodent studies and offers a more coherent interpretation of species differences. Furthermore, this developmental stage–dependent framework can be extended across the lifespan. Brain structures undergo functional changes not only during development but also during aging; however, these changes do not reflect a single neural mechanism operating continuously or simultaneously across time. Rather, distinct neurobiological processes at different life stages may differentially shape resilience or vulnerability to stress. This perspective also provides a biological rationale for considering the timing of interventions, as neural processes engaged by stress differ across developmental stages. Integrating developmental timing into the experimental design and analysis is essential for clarifying causal mechanisms and improving the translational relevance of early-life stress models to human neuropsychiatric vulnerability.

Appendices and Nomenclature

PND	Postnatal day
SHRP	Stress hyporesponsive period
CORT	Corticosterone
HPA	axis Hypothalamic–Pituitary–Adrenal axis
BDNF	Brain-derived neurotrophic factor
GR	Glucocorticoid receptor
c-Fos	Protein marker of neuronal activity
ADHD	Attention deficit hyperactivity disorder

Experimental paradigms

- Early weaning – Permanent separation from the dam before natural weaning
- Limited bedding/Nesting model – Environmental stress paradigm reducing maternal care
- Maternal separation – Daily separation of pups from the dam for a defined period

Behavioral outcomes

- Anxiety-like behavior – Behavioral assays reflecting elevated fear or avoidance
- Depression-like behavior – Behavioral assays reflecting decreased motivation or reward-seeking

Neural measures

- Dendritic spine density – Indicator of synaptic connectivity

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Conflict of Interest

The author declares no conflict of interest.

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Chapter 3

Cardiovascular Manifestations of Anxiety Disorders: Translational Insights from Neuroradiology

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Abstract

Anxiety disorders are highly prevalent psychiatric conditions with a significant, bidirectional link to cardiovascular disease (CVD). Translational research has elucidated the complex neurobiological, autonomic, and inflammatory pathways that mediate this relationship. Chronic anxiety leads to persistent activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. This results in elevated catecholamines and cortisol, driving endothelial dysfunction, oxidative stress, and systemic inflammation. These processes collectively contribute to the development of hypertension, arrhythmias, myocardial ischemia, and stress-induced cardiomyopathy. This chapter explores the neurocardiac axis, detailing how alterations in brain circuits (e.g., amygdala, insula, prefrontal cortex) translate into cardiovascular pathology. We examine the diagnostic and prognostic value of translational biomarkers, including heart rate variability, inflammatory mediators, and neuroimaging findings. The overlap between anxiety and cardiac symptoms presents a diagnostic challenge. Recognizing these links is crucial for early detection, risk stratification, and holistic care. We emphasize integrative “psychocardiology” approaches, bridging psychiatry and cardiology with combined pharmacological and behavioral interventions. Synthesizing this bench-to-bedside evidence underscores the need for interdisciplinary strategies to improve patient outcomes.

Keywords: anxiety disorders, neurocardiology, brain-heart axis, autonomic dysfunction, HPA axis, translational research, psychocardiology, cardiovascular risk

1. Introduction

1.1 Overview of anxiety disorders and global burden

Anxiety disorders are among the most common mental health conditions, affecting hundreds of millions of people across the world. They include generalized anxiety

disorder (GAD), panic disorder, social anxiety disorder, and other forms of excessive fear or worry that interfere with daily life. Although anxiety is a natural human response to stress, when it becomes persistent or overwhelming, it can lead to long-term physical and psychological consequences. One area that has received growing attention is the impact of anxiety on the cardiovascular system – the heart and blood vessels responsible for circulating blood throughout the body. Symptoms such as palpitations, chest tightness, or shortness of breath reflect real physiological changes triggered by the body's stress response. Understanding how anxiety influences cardiovascular function helps explain why people with chronic anxiety face higher risks of heart disease, high blood pressure, and irregular heart rhythms.

1.2 Epidemiological association between anxiety and cardiovascular disease

Large population-based studies have consistently shown that individuals with anxiety disorders have a greater likelihood of developing cardiovascular disease (CVD) compared to those without anxiety [1]. This association persists even after adjusting for lifestyle factors such as smoking, diet, and exercise. The physiological explanation lies in the body's "fight-or-flight" response – a survival mechanism that increases heart rate, blood pressure, and stress hormone levels during perceived danger. When this response becomes chronic, it can overwork the heart, damage blood vessels, and promote inflammation. Furthermore, anxiety can worsen outcomes in people who already have heart conditions. Patients recovering from myocardial infarction, for example, often experience heightened anxiety, which can delay recovery and increase the risk of recurrent cardiac events [2]. This interplay between emotional distress and cardiovascular health has led researchers to explore the mechanisms that connect the brain and heart.

1.3 Evolution of translational research in neurocardiology

The field of neurocardiology has emerged to study the bidirectional communication between the nervous and cardiovascular systems. Translational research – which aims to apply laboratory discoveries to patient care – has been central to this development. Basic science studies in animals have demonstrated that chronic stress and anxiety alter brain regions such as the amygdala and hypothalamus, resulting in hormonal and autonomic changes that affect the heart [3]. Clinical studies have mirrored these findings, showing that patients with anxiety display abnormal heart rate variability (HRV), elevated stress hormones, and distinctive brain activity patterns on imaging [4]. By integrating neuroscience, endocrinology, and cardiology, translational neurocardiology helps explain how psychological factors can produce measurable physical effects. This approach not only advances scientific understanding but also opens new pathways for prevention and treatment.

1.4 Objectives and scope of the chapter

This chapter aims to bridge knowledge from basic neuroscience and clinical cardiology to explain how anxiety influences heart function and contributes to CVD. It describes the key biological pathways that connect the brain to the heart, including the autonomic nervous system (ANS), hormonal stress responses, and inflammatory mechanisms.

By presenting these topics in a translational framework – “from bench to bedside” – the chapter seeks to help clinicians, researchers, and general readers appreciate how emotional health and cardiovascular health are deeply interconnected. Understanding this relationship can guide early detection, integrated care, and innovative treatment strategies for patients affected by both anxiety and cardiovascular disorders.

2. Translational mechanisms linking anxiety and cardiovascular disorders (Part I: From brain to heart – pathophysiological pathways)

Anxiety disorders exert profound effects on the cardiovascular system through an intricate network of neuroendocrine, autonomic, and inflammatory mechanisms. Translational research has revealed that chronic anxiety alters the function of key neural circuits and stress-response pathways, leading to measurable cardiac consequences.

2.1 The neurocardiac axis: Integration of central and peripheral pathways

The intimate relationship between the brain and the heart is far more than a metaphor – it is a measurable biological reality known as the neurocardiac axis. This axis represents a continuous feedback network through which the brain regulates cardiac function and, in turn, the heart sends sensory information back to the brain. At the core of this system lies the limbic network, a collection of brain regions responsible for processing emotions, motivation, and stress responses. The amygdala interprets fear and threat, the insula integrates visceral sensations, and the anterior cingulate cortex (ACC) modulates emotional decision-making and autonomic tone. These regions communicate extensively with the hypothalamus, the body’s main command center for hormonal and autonomic regulation. From the hypothalamus, signals descend through the brainstem, particularly the nucleus tractus solitarius (NTS) and rostral ventrolateral medulla (RVLM), which directly influence the sympathetic and parasympathetic branches of the ANS. Conversely, the heart is not merely a passive recipient of these signals. Specialized baroreceptors in the aorta and carotid sinus detect blood pressure changes and send feedback via the vagus nerve to the brainstem, influencing mood and emotional regulation. This bottom-up communication explains why cardiac sensations – such as palpitations or chest tightness – can intensify anxiety, forming a self-reinforcing loop between emotion and physiology. In anxiety disorders, chronic overactivation of the neurocardiac axis leads to sympathetic hyperreactivity, reduced vagal tone, and neuroendocrine dysregulation. These alterations translate into measurable cardiovascular consequences, such as elevated resting heart rate, increased arterial stiffness, and endothelial injury.

2.2 Autonomic nervous system dysregulation in anxiety

The ANS serves as the body’s rapid-response communication network, maintaining balance between internal organs and external demands. In anxiety disorders, the brain’s perception of threat chronically activates the SNS while simultaneously suppressing the PNS. Translational studies have consistently shown

that this dysregulation serves as a key biological link between emotional distress and cardiac morbidity.

2.2.1 Sympathetic overactivity and parasympathetic withdrawal

The sympathetic nervous system (SNS) releases adrenaline (epinephrine) and noradrenaline (norepinephrine) from nerve endings and the adrenal medulla. While beneficial during acute stress, chronic sympathetic overdrive – as seen in anxiety – induces continuous hemodynamic stress on the cardiovascular system. Persistent sympathetic activation results in:

- Tachycardia and elevated blood pressure due to prolonged catecholamine exposure.
- Increased oxidative stress, damaging vascular endothelium, and promoting atherosclerosis.
- Altered electrical activity in the myocardium, predisposing to arrhythmias.

Simultaneously, there is parasympathetic withdrawal, primarily mediated by reduced vagal tone. The loss of this protective modulation heightens cardiac workload and impairs the body's ability to return to baseline after emotional arousal. The combined effect is a physiological environment characterized by sympathetic dominance, in which even minor stressors trigger exaggerated cardiovascular responses.

2.2.2 Heart rate variability as a translational biomarker

One of the most important clinical tools to assess autonomic imbalance is HRV – the natural fluctuation in the time intervals between consecutive heartbeats [5]. Contrary to common intuition, a healthy heart does not beat with machine-like regularity; instead, subtle variability reflects the heart's adaptability and resilience. In anxiety disorders, HRV is consistently reduced, indicating diminished vagal influence and excessive sympathetic drive. Low HRV has emerged as a translational biomarker linking psychological distress to cardiovascular vulnerability. Research has demonstrated that individuals with persistently low HRV are at increased risk for:

- Arrhythmias (especially atrial fibrillation [AF] and ventricular ectopy)
- Hypertension and coronary artery disease
- Sudden cardiac death in severe cases

Moreover, HRV offers a powerful, noninvasive window into the mind–heart connection. Interventions such as biofeedback training, mindfulness meditation, aerobic exercise, and vagus nerve stimulation have been shown to improve HRV, supporting the concept that restoring autonomic balance can improve both mental well-being and cardiovascular outcomes.

2.3 Hypothalamic–pituitary–adrenal axis activation and cortisol effects

The hypothalamic–pituitary–adrenal (HPA) axis is the body's central stress-response system. It acts as a powerful hormonal bridge between psychological stress and physical health. Under normal conditions, the HPA axis operates as a self-regulating feedback loop. However, in chronic anxiety, this feedback loop becomes dysregulated. The brain remains in a persistent state of perceived threat, continuously stimulating cortisol release. Prolonged exposure to high cortisol levels has widespread effects on cardiovascular physiology:

- Endothelial dysfunction: cortisol reduces nitric oxide availability, impairing vessel dilation and increasing vascular stiffness.
- Hypertension: sustained cortisol elevation promotes sodium retention and enhances vascular reactivity.
- Metabolic alterations: cortisol drives insulin resistance, abdominal obesity, and dyslipidemia – all potent cardiovascular risk factors.
- Myocardial effects: excess cortisol weakens cardiac muscle fibers, increases oxidative stress, and interferes with calcium handling, leading to impaired contractility and structural remodeling.

This state of chronic stress-induced cardiotoxicity highlights the direct biochemical translation of anxiety into measurable cardiovascular pathology.

2.3.1 Mechanisms of chronic stress-induced cardiotoxicity

Translational research has demonstrated that prolonged activation of the HPA axis alters cardiac gene expression, promotes inflammation, and accelerates aging-related vascular changes. Elevated cortisol levels upregulate proinflammatory cytokines (IL-6, TNF- α), enhance oxidative stress, and disrupt mitochondrial energy metabolism in cardiac cells. These biochemical disturbances contribute to atherosclerosis, arrhythmogenic vulnerability, and left ventricular hypertrophy. Moreover, high cortisol suppresses endothelial progenitor cell activity, impairing vascular repair and angiogenesis. Over time, this results in microvascular dysfunction – one of the earliest signs of stress-related heart disease.

2.3.2 Translational animal models of neuroendocrine dysregulation

Animal studies provide critical insight into the mechanistic links between anxiety, HPA axis activation, and cardiovascular injury. Rodent models exposed to chronic unpredictable stress (CUS), social isolation, or restraint stress show sustained corticosterone elevation (the rodent equivalent of cortisol) [6]. This is accompanied by:

- Cardiac hypertrophy and fibrosis occur due to excessive glucocorticoid receptor (GR) stimulation.

- Autonomic imbalance, with reduced baroreceptor sensitivity and diminished vagal tone.

Altered expression of stress-related genes, such as GR and mineralocorticoid receptor (MR) genes, mirrors changes seen in human patients with anxiety and depression. Such translational models are invaluable for identifying therapeutic targets.

2.4 Neuroinflammation and endothelial dysfunction

One of the most striking translational discoveries in neurocardiology is the realization that chronic stress and anxiety activate the immune system, triggering persistent low-grade inflammation that directly harms the cardiovascular system. The bridge between mental distress and vascular disease lies in two interconnected processes: neuroinflammation (inflammation within the brain and central nervous system) and endothelial dysfunction (impaired functioning of the inner lining of blood vessels). Together, these create a harmful feedback loop that amplifies both emotional and cardiovascular pathology. In a healthy state, the endothelium maintains vascular tone, prevents clot formation, and regulates immune cell trafficking. However, under prolonged stress, sympathetic activation and elevated cortisol levels stimulate the release of proinflammatory cytokines – such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and C-reactive protein (CRP) – from immune cells and endothelial tissues.

2.4.1 Cytokine-mediated vascular injury

Persistent elevation of cytokines creates a biochemical environment that injures the vascular endothelium. Cytokines promote:

- Endothelial activation leads to the expression of adhesion molecules that attract white blood cells to vessel walls.
- Reduction of nitric oxide (NO) bioavailability, which impairs vasodilation and promotes vascular stiffness.
- Prothrombotic changes increase platelet aggregation and the risk of clot formation.
- Oxidative stress results in free-radical damage to lipids, proteins, and DNA within vascular cells.

These molecular events set the stage for atherosclerosis, coronary microvascular dysfunction, and even acute coronary syndromes. Translational studies have demonstrated elevated levels of IL-6 and CRP in patients with GAD and posttraumatic stress disorder (PTSD), correlating strongly with markers of arterial stiffness and carotid intima-media thickness.

2.4.2 Blood–brain barrier and systemic inflammation links

The blood–brain barrier (BBB) acts as a selective shield between the central nervous system and the bloodstream. However, chronic anxiety and systemic

inflammation can disrupt BBB integrity, leading to a “leaky barrier” phenomenon [7]. When inflammatory cytokines and activated immune cells cross the BBB, they trigger neuroinflammatory cascades within regions responsible for emotion and autonomic regulation, including the amygdala, hippocampus, and prefrontal cortex. This neural inflammation enhances stress reactivity and sympathetic output, which, in turn, further exacerbates endothelial injury – a vicious cycle of mind–body inflammation. Experimental models show that stress-induced glucocorticoid surges alter the structure of tight junction proteins (such as claudin and occludin) within the BBB, weakening its selective permeability.

2.5 Neuroimaging and neurobiological evidence of brain–heart interaction

Over the past two decades, advances in neuroimaging have transformed our understanding of how emotional and physiological processes intertwine. Modern imaging tools – particularly functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) – have provided powerful translational insights into how anxiety alters brain circuits and, in turn, affects cardiovascular regulation.

2.5.1 Amygdala hyperactivity and cardiovascular outcomes

The amygdala, a key center for fear and emotional processing, plays a pivotal role in translating psychological stress into physiological arousal. Neuroimaging studies have shown that heightened amygdala activity is associated with increased sympathetic drive, leading to elevated heart rate, blood pressure, and vascular resistance [3]. In a landmark PET study, individuals with greater resting amygdala activity demonstrated higher systemic inflammation and a greater incidence of cardiovascular events – even after controlling for traditional risk factors. This suggests that emotional stress can biologically “prime” the cardiovascular system for disease. Additionally, chronic amygdala hyperactivity has been linked to increased bone marrow activity, resulting in enhanced leukocyte production and subsequent vascular inflammation – a novel mechanistic bridge between anxiety and atherosclerosis.

2.5.2 Translational relevance of fMRI and PET findings

Functional imaging provides not only diagnostic insight but also translational value for therapeutic research. Using fMRI, scientists can visualize real-time changes in brain regions like the ACC and insula, both of which modulate autonomic tone and cardiovascular control. Reduced connectivity between these regions and the prefrontal cortex has been observed in individuals with anxiety, reflecting weakened top-down regulation of emotional responses and heart rate control. PET imaging, through radiotracer mapping, has further revealed that heightened metabolic activity in the amygdala and ACC correlates with increased arterial inflammation, offering a biological link between stress, neural activation, and vascular disease progression. These imaging biomarkers serve as valuable tools to identify high-risk patients and evaluate the effectiveness of interventions.

3. Clinical manifestations and translational evidence (Part II: From mechanism to bedside – clinical correlates)

3.1 Anxiety-related cardiovascular syndromes

The pathophysiological pathways of anxiety translate into several specific cardiovascular conditions.

3.1.1 Hypertension and autonomic imbalance

Persistent activation of the SNS in anxious individuals leads to sustained vasoconstriction, tachycardia, and elevated cardiac output. These physiological effects, when prolonged, result in neurogenic hypertension. Studies have shown that patients with GAD and panic disorder often exhibit higher plasma norepinephrine and epinephrine levels than nonanxious controls [8]. Chronic sympathetic overdrive also suppresses baroreceptor sensitivity and diminishes parasympathetic (vagal) tone, preventing normal cardiovascular recovery after stress. This imbalance contributes to increased blood pressure variability, an established risk factor for vascular injury and atherosclerosis.

Translationally, anxious hypertensive patients often present with “white coat hypertension,” exaggerated BP responses during clinical evaluation, and resistance to standard antihypertensive therapy until the underlying anxiety is managed.

3.1.2 Cardiac arrhythmias and palpitations

Anxiety frequently manifests with palpitations, which may reflect both subjective awareness of normal heartbeats and actual arrhythmic events. The sympatho-vagal imbalance in anxiety disrupts normal cardiac electrophysiology, predisposing individuals to sinus tachycardia, premature ventricular contractions, and even AF [9]. Mechanistically, heightened catecholamine release during panic episodes increases intracellular calcium influx, thereby enhancing myocardial excitability and triggering ectopic depolarizations. Neuroimaging and autonomic studies reveal that reduced HRV – a marker of poor vagal control – is a consistent feature in anxious individuals [10]. Low HRV predicts both arrhythmia susceptibility and sudden cardiac death. Importantly, these arrhythmic tendencies are biologically mediated, reversible phenomena that normalize with effective treatment of anxiety.

3.1.3 Myocardial ischemia and stress cardiomyopathy

Perhaps the most striking example of the brain–heart connection is Takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy or “broken heart syndrome.” This condition mimics acute coronary syndrome, with chest pain, ST-segment elevation, and elevated cardiac enzymes; yet, coronary angiography reveals no obstructive lesions.

The underlying mechanism involves excessive sympathetic activation and a surge in catecholamines, leading to transient left ventricular apical ballooning and contractile dysfunction. Imaging studies confirm that these patients often have heightened amygdala activity prior to the cardiac event, supporting the role of

emotional stress in its pathogenesis [11]. In less dramatic forms, chronic anxiety also contributes to microvascular ischemia through endothelial dysfunction, platelet activation, and increased inflammatory cytokines. Translational work has shown that sustained stress impairs nitric oxide bioavailability, leading to impaired coronary flow reserve and ischemia even in the absence of significant plaque burden.

3.2 Clinical biomarkers and diagnostic approaches

Understanding how anxiety translates into cardiovascular dysfunction requires measuring the physiological signatures of this brain–heart interaction.

3.2.1 Autonomic and neuroendocrine biomarkers

The most validated noninvasive biomarker of autonomic imbalance is HRV.

- HRV reflects the variation in time intervals between heartbeats. Lower HRV is consistently associated with higher anxiety severity and greater cardiovascular morbidity.
- Reduced HRV indicates diminished vagal (parasympathetic) modulation of the heart and heightened sympathetic dominance – a hallmark of chronic stress states. In addition, plasma catecholamines (epinephrine, norepinephrine) and cortisol levels serve as biochemical indicators of sympathetic and HPA axis activation. Persistent elevation of these biomarkers correlates with hypertension, endothelial dysfunction, and metabolic disturbances in anxious patients [12].

3.2.2 Inflammatory and endothelial markers

Emerging evidence positions chronic low-grade inflammation as a critical mediator between anxiety and CVD. Psychological stress triggers cytokine release (IL-6, TNF- α , CRP), which induces endothelial activation and vascular stiffness.

- Elevated CRP levels have been documented in individuals with panic disorder and PTSD.
- IL-6 serves as a dual biomarker – reflecting both systemic inflammation and neural stress responses.
- Increased expression of cell adhesion molecules (VCAM-1, ICAM-1) in endothelial cells suggests early vascular injury driven by neurohumoral stress.

3.2.3 Imaging and functional diagnostics

Recent technological advances have expanded diagnostic possibilities beyond traditional cardiac testing.

- fMRI highlights increased activity in the amygdala, ACC, and insula in patients with anxiety – regions implicated in autonomic regulation.

- Parallel echocardiographic and cardiac MRI studies show transient myocardial dysfunction during acute anxiety episodes, supporting a neurocardiac feedback mechanism.
- PET scans demonstrate a link between heightened amygdala activity and increased arterial inflammation, suggesting a measurable neural trigger for vascular disease.

For bedside application, electrocardiography (ECG) remains indispensable. Subtle ECG changes – such as sinus tachycardia, QTc prolongation, and increased T-wave variability – may indicate sympathetic dominance.

3.3 Therapeutic implications and translational interventions

The growing understanding of the brain–heart connection has paved the way for therapeutic strategies that target both psychological and cardiovascular pathways simultaneously.

3.3.1 Pharmacologic interventions

Pharmacologic strategies must address both psychological distress and autonomic dysregulation. Selective serotonin reuptake inhibitors (SSRIs) remain first-line agents for generalized anxiety and panic disorders, with evidence suggesting they improve HRV [13] and reduce resting heart rate over time [14]. By increasing central serotonin levels, SSRIs reduce limbic overactivation (especially in the amygdala), thereby modulating sympathetic output. Benzodiazepines, though effective for acute anxiety and palpitations, are best reserved for short-term use due to dependency risks. Beta-blockers (e.g., propranolol, atenolol) bridge psychiatry and cardiology by blunting adrenergic overactivity. They are especially useful in performance anxiety, panic attacks, or postmyocardial infarction patients with anxiety-related tachyarrhythmias.

3.3.2 Behavioral and psychotherapeutic interventions

Cognitive and behavioral therapies remain cornerstones of nonpharmacological treatment. Cognitive behavioral therapy (CBT) and mindfulness-based stress reduction (MBSR) have demonstrated measurable cardiovascular benefits – including reductions in blood pressure, heart rate, and inflammatory biomarkers [15].

Neuroimaging studies show that CBT normalizes amygdala and ACC activity, reinforcing prefrontal control over emotional processing. This restores autonomic balance and decreases sympathetic tone.

Biofeedback and HRV-guided training represent direct translational applications – patients learn to consciously modulate autonomic output by tracking their HRV in real time. Such techniques enhance parasympathetic tone, reduce anxiety severity, and improve sleep and blood pressure regulation.

3.3.3 Integrated lifestyle and preventive approaches

Lifestyle interventions provide the physiological foundation for anxiety and cardiovascular control. Regular aerobic exercise not only enhances mood through

endorphin release but also increases vagal tone and endothelial nitric oxide production, improving vascular function. A Mediterranean-style diet, rich in omega-3 fatty acids, antioxidants, and polyphenols, helps reduce both systemic inflammation and stress-related lipid abnormalities [16]. Sleep regulation, social support, and structured daily routines stabilize circadian cortisol rhythms, preventing chronic HPA axis activation.

3.4 Comorbidity and diagnostic challenges

3.4.1 Overlapping symptoms between anxiety and cardiac disorders

The clinical overlap between anxiety and CVDs presents a major diagnostic challenge. Both conditions share a spectrum of symptoms – such as palpitations, chest tightness, breathlessness, dizziness, sweating, and fatigue – that stem from autonomic hyperactivity and heightened sympathetic drive. Physiologically, anxiety-induced sympathetic activation mimics early manifestations of cardiac disease by increasing heart rate, contractility, and peripheral resistance. Conversely, anxiety symptoms may mask or exacerbate genuine cardiovascular pathology – such as unstable angina – through heightened pain perception and stress-mediated vasoconstriction. This bidirectional overlap is compounded by shared biological mechanisms, including autonomic dysregulation, elevated catecholamines, HPA axis overactivity, and systemic inflammation, all of which contribute to both anxiety and cardiovascular morbidity.

3.4.2 Clinical misinterpretation and implications for patient care

Clinical misinterpretation of anxiety-related cardiac symptoms is a well-documented problem. When physical symptoms are prematurely labeled as “psychogenic,” patients risk being underdiagnosed for cardiac disease; conversely, when anxiety symptoms are interpreted as cardiac pathology, they may undergo unnecessary investigations or interventions. In cardiology settings, subtle psychological distress is often underrecognized, leading to suboptimal outcomes. Anxiety can independently worsen prognosis after acute coronary syndromes, influence medication adherence, and increase rehospitalization rates. Psychocardiology – an emerging interdisciplinary field – emphasizes integrating mental health evaluation into cardiovascular care.

Screening tools such as the Hospital Anxiety and Depression Scale (HADS) or the generalized anxiety disorder-7 (GAD-7) can identify comorbid anxiety early, enabling timely interventions.

4. Translational management strategies (Part III: From evidence to practice – integrative care models)

4.1 Early detection and risk stratification

The intersection between anxiety disorders and CVD demands a translational management approach that bridges psychological assessment with physiological monitoring. Early detection of anxiety in cardiac patients – and

vice versa – is vital for timely intervention and prevention of adverse outcomes. Clinical and translational research increasingly supports the role of multidimensional risk assessment, which combines traditional cardiovascular risk factors (hypertension, diabetes, dyslipidemia) with psychological and autonomic markers of stress. Chronic anxiety amplifies sympathetic tone, elevates cortisol, and induces low-grade inflammation, all of which accelerate atherosclerosis and impair endothelial function. From a translational standpoint, neurocardiac biomarkers – including HRV, cortisol levels, and inflammatory cytokines (IL-6, TNF- α) – provide an objective window into the mind–heart interface. HRV, in particular, serves as a reliable physiological marker for autonomic balance and emotional regulation. Reduced HRV has been consistently associated with both anxiety disorders and elevated cardiovascular risk, making it a powerful screening tool for early detection and risk stratification [10].

4.1.1 Screening tools and heart rate variability monitoring

HRV monitoring provides a noninvasive, quantitative measure of autonomic function and emotional stress. HRV represents the beat-to-beat variation in heart rate, controlled by the balance between sympathetic and parasympathetic inputs. Anxiety disorders typically exhibit reduced HRV, reflecting autonomic rigidity and diminished vagal tone.

Technological advancements – such as wearable sensors, mobile ECG devices, and smartphone-based HRV applications – now allow real-time tracking of stress responses in both clinical and ambulatory settings [17]. These digital tools bridge the gap between translational research and bedside practice, helping physicians correlate psychological distress with physiological markers. Furthermore, longitudinal HRV assessment can track the efficacy of therapeutic interventions, such as relaxation training, mindfulness, or pharmacotherapy, providing objective biofeedback on the recovery of autonomic balance.

4.1.2 Integrating mental health evaluation into cardiology clinics

Despite the robust evidence linking anxiety with cardiovascular morbidity, mental health assessment remains underutilized in cardiology practice. Traditional models of care often separate “mind” and “heart” domains, leading to fragmented management. However, the translational paradigm emphasizes integration over isolation – recognizing that effective cardiovascular care must encompass psychological well-being. The integration process begins with routine mental health screening during cardiology visits, followed by multidisciplinary collaboration between cardiologists, psychiatrists, and clinical psychologists. This ensures that patients with anxiety or depressive symptoms receive early counseling, CBT, or stress-reduction interventions alongside conventional cardiac management. Clinics that implement integrated care models report improved medication adherence, reduced readmission rates, and enhanced quality of life [18]. Interventions such as MBSR, biofeedback, and cardiac rehabilitation programs incorporating relaxation and physical activity further strengthen heart–brain resilience.

4.2 Pharmacological interventions and translational perspectives

4.2.1 Role of anxiolytics and antidepressants in cardiovascular safety

Pharmacological management of anxiety disorders in patients with CVD requires a delicate balance between psychological efficacy and cardiovascular safety. Traditional anxiolytics, particularly benzodiazepines (e.g., alprazolam, lorazepam), remain among the most effective short-term agents for acute anxiety relief. They exert their action by enhancing gamma-aminobutyric acid (GABA) neurotransmission, thereby reducing central nervous system excitability and sympathetic drive. However, long-term benzodiazepine use is associated with dependence, cognitive impairment, and altered sleep architecture, and it may worsen depression or respiratory function in vulnerable individuals. Thus, the preferred pharmacologic agents for chronic anxiety with cardiovascular comorbidity are SSRIs and serotonin–norepinephrine reuptake inhibitors (SNRIs). SSRIs such as sertraline, escitalopram, and citalopram have demonstrated favorable cardiovascular profiles, showing neutral or beneficial effects on HRV, platelet function, and endothelial health [14]. Among these, sertraline has been the most extensively studied in postmyocardial infarction depression and anxiety, showing improvements in both mood and cardiac prognosis. Conversely, tricyclic antidepressants (TCAs) such as amitriptyline should be avoided due to their arrhythmogenic and anticholinergic effects [19].

4.2.2 Pharmacogenomic insights into anxiolytic response

The variability in response to anxiolytic and antidepressant therapy among patients with comorbid anxiety and CVD reflects a pharmacogenomic dimension of psychocardiology. Gene variants affecting serotonin transporters (SLC6A4), CYP450 enzymes (especially CYP2C19 and CYP2D6), and neurotrophic factors (brain-derived neurotrophic factor [BDNF]) influence both therapeutic efficacy and side effect profiles. For instance, carriers of the short allele of the 5-HTTLPR polymorphism in SLC6A4 exhibit exaggerated amygdala reactivity, greater autonomic arousal, and reduced responsiveness to SSRIs. Similarly, CYP2C19 poor metabolizers accumulate higher plasma concentrations of citalopram and escitalopram, increasing the risk of QT prolongation – an especially relevant issue for cardiac patients [20]. From a translational standpoint, pharmacogenomic profiling enables personalized treatment selection – optimizing drug choice, dosage, and monitoring based on a patient's genetic makeup.

4.2.3 Cardioprotective potential of antiinflammatory and autonomic modulators

A compelling translational frontier lies in repurposing antiinflammatory and autonomic modulators for the dual management of anxiety and cardiovascular dysfunction. Chronic anxiety fosters a proinflammatory milieu, characterized by elevated cytokines (IL-1 β , IL-6, TNF- α) and oxidative stress, which contribute to endothelial damage, atherosclerosis, and arrhythmogenesis.

Emerging evidence suggests that agents with antiinflammatory or sympatholytic properties – such as beta-blockers, omega-3 fatty acids, and statins – may offer adjunctive anxiolytic benefits. Beta-blockers like propranolol not only attenuate

somatic anxiety symptoms (palpitations, tremor) but also reduce sympathetic outflow and catecholamine-induced myocardial stress. Similarly, omega-3 fatty acids modulate membrane fluidity and serotonin receptor function, supporting both cardiac and emotional stability. Novel research also implicates anticytokine therapies (e.g., IL-6 inhibitors like tocilizumab) in reducing systemic inflammation linked to anxiety and depression in CVD patients. Furthermore, vagal nerve stimulation (VNS) and bioelectronic neuromodulation – by restoring parasympathetic dominance – show promise as nonpharmacological interventions with both cardioprotective and anxiolytic effects.

4.3 Nonpharmacological and integrative approaches

While pharmacological therapy plays a key role, nonpharmacological interventions represent an equally crucial pillar in translational care. These approaches bridge the gap between psychological well-being and cardiovascular physiology, emphasizing mind–body integration and autonomic rebalancing.

4.3.1 Cognitive Behavioral Therapy and biofeedback

CBT remains the gold standard psychological treatment for anxiety disorders and has shown strong translational applicability in cardiology. By restructuring maladaptive thought patterns, CBT alleviates anxiety-driven sympathetic activation, thereby reducing heart rate, blood pressure, and perceived stress. Studies in postmyocardial infarction patients demonstrate that CBT significantly improves HRV and decreases recurrent cardiac events, indicating its cardioprotective value [15]. Biofeedback, particularly HRV biofeedback, enhances this effect by providing patients with real-time information about their autonomic state. Through guided breathing and relaxation techniques, patients learn to consciously increase vagal tone and stabilize cardiovascular rhythms.

4.3.2 Mindfulness-based and stress reduction programs

MBSR, meditation, and yoga practices have gained scientific recognition as evidence-based tools for modulating neuroendocrine and cardiovascular responses. These interventions lower amygdala hyperactivity, suppress HPA axis overdrive, and restore parasympathetic dominance, thereby mitigating stress-related cardiovascular risk [21]. Functional neuroimaging studies demonstrate increased prefrontal–amygdala connectivity and decreased cortisol secretion following sustained mindfulness practice. Clinically, MBSR interventions lead to improvements in blood pressure, resting heart rate, and endothelial function in patients with coronary artery disease and hypertension.

4.3.3 Lifestyle interventions and patient education

Lifestyle modification remains the cornerstone of both cardiovascular and anxiety management. Regular aerobic exercise reduces anxiety symptoms, increases BDNF, and improves endothelial and autonomic function. Similarly, adherence to antiinflammatory dietary patterns, such as the Mediterranean diet, lowers systemic inflammation and improves emotional regulation through the gut–brain axis.

Adequate sleep, smoking cessation, and moderation of caffeine or alcohol intake further contribute to neurocardiac stability. Integrating structured patient education within cardiac rehabilitation programs ensures sustained behavioral change and empowers individuals to actively participate in their recovery.

5. Conclusion

Anxiety disorders and CVDs share a deeply interconnected relationship, bridged by overlapping neurobiological, autonomic, and inflammatory pathways. Over the past two decades, translational research has shifted our understanding of anxiety from a purely psychological condition to one that exerts profound effects on the cardiovascular system through mechanisms such as chronic sympathetic activation, HPA axis dysregulation, and neuroinflammation. These discoveries have underscored the existence of a **neurocardiac axis** – a dynamic communication network between the brain and heart that influences both emotional regulation and cardiovascular health.

From a **translational perspective**, the clinical relevance of these findings is profound. Anxiety-related cardiovascular syndromes – ranging from hypertension and arrhythmias to stress-induced cardiomyopathy – highlight the need for integrated care models that combine psychiatric, neurological, and cardiological expertise. Identifying anxiety as a modifiable cardiovascular risk factor allows clinicians to intervene early through screening tools, HRV monitoring, and mental health assessments integrated within cardiology settings.

Moreover, emerging **pharmacogenomic and biomarker research** is paving the way toward personalized medicine, enabling clinicians to predict which patients may respond best to anxiolytics, antidepressants, or stress-reducing therapies based on genetic and neuroendocrine profiles. Complementary nonpharmacological interventions – such as CBT, mindfulness training, and lifestyle modification – further strengthen this holistic approach, offering both preventive and therapeutic benefits.

Looking forward, the **future of neurocardiology** lies in bridging the gap between laboratory discoveries and bedside applications. Collaborative, interdisciplinary research must continue to refine our molecular understanding of the brain–heart connection while developing integrative care strategies that place patient well-being at the center. Ultimately, recognizing and managing anxiety as both a mental and cardiovascular condition will redefine preventive cardiology and improve outcomes for millions worldwide.

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Chapter 4

Dental Anxiety: Understanding Psychophysiological Responses in Routine Periodontal Care

Ruchi Ramanujan and Rahul Bhandary

Abstract

Dental anxiety remains one of the most common yet underestimated barriers to oral healthcare, directly influencing both patient compliance and long-term treatment outcomes. This chapter expands upon insights from a previously published study by the authors, using it as a clinical anchor to explore broader psychophysiological and behavioral dimensions of dental apprehension in the context of routine periodontal care. The study, conducted at A.B. Shetty Memorial Institute of Dental Sciences, Mangalore, involved an assessment of anxiety levels in adult patients before and after scaling and polishing procedures. It revealed notable gender-based variations, the influence of prior dental experiences, and the modulatory role of periodontal interventions on anxiety perception. To further contextualise these findings and reinforce their relevance across populations, a synthesis of recent studies from national and international literature has been incorporated in the form of a structured summary table. This comparative overview strengthens the evidence base and highlights recurring patterns of anxiety in periodontal care. Beyond the immediate clinical context, this chapter bridges dentistry and mental health research, positioning dental anxiety not merely as a procedural response but as part of the broader anxiety spectrum, shaped by perception, memory, and neurobiological predisposition. The discussion further considers strategies for anxiety reduction through empathetic communication, behavioural conditioning, and patient-centred care, aligning with translational perspectives on anxiety management within healthcare systems.

Keywords: dental anxiety, apprehension, oral prophylaxis, scaling and polishing, periodontal health, behavioral response, psychophysiology, patient perception

1. Introduction

Dental anxiety remains one of the most persistent and clinically relevant challenges in dentistry, shaping how patients perceive, experience, and engage with oral healthcare. Unlike generalised anxiety, dental apprehension is uniquely environmental: it originates not only from pain but also from anticipation, vulnerability, sensory cues, and memory. In periodontal care, where prevention,

maintenance, and repetitive contact are integral to health stability, anxiety becomes far more than an emotional inconvenience; it becomes a determinant of disease behaviour, attendance patterns, and treatment success.

Routine periodontal procedures such as scaling and polishing are traditionally categorised as ‘on-threatening’. However, from a patient’s perspective, these procedures often represent invasive sensations, instrument contact with delicate tissues, unfamiliar auditory stimuli, and perceived bleeding – all of which have the potential to trigger apprehension. Understanding this anxiety is, therefore, essential not only for improving patient comfort but also for ensuring long-term periodontal stability and ethical, patient-centred care.

Indeed, epidemiological studies indicate that roughly 10%–20% of people experience significant dental fear or anxiety, which can complicate dental treatment, and about two-thirds of those affected are female. Severe cases, approximately 2%–3% of adults, meet the criteria for dental phobia, a clinical condition marked by intense fear and avoidance of dental care [1]. This prevalence underscores that dental anxiety is not a rare phenomenon but a widespread barrier to care.

This chapter builds on a previously published investigation focused on anxiety levels before and after routine scaling and polishing procedures among adult dental patients [2] and expands the scope of interpretation by embedding it within a broader psychophysiological framework. Readers will explore how anxiety manifests not only behaviourally but also through biological substrates that influence pain thresholds, healing capacity, and treatment cooperation. Emotional memory, cognitive conditioning, and individual patient predispositions will be discussed as central components shaping dental fear.

Further, the narrative moves beyond theoretical exploration to offer practical clinical insight, detailing how anxiety can be identified, communicated about, and managed effectively during periodontal care. From behavioural techniques and communication strategies to procedural adjustments and support-based conditioning, this work advocates for dentistry that is both technically proficient and emotionally intelligent. It invites readers to view dental anxiety not as a hurdle to treatment, but as a modifiable determinant that holds the key to truly patient-centred care.

2. Psychophysiological dimensions of dental anxiety in routine periodontal care

2.1 Conceptual understanding of dental anxiety in periodontal settings

Dental anxiety represents an emotional and physiological response triggered by an anticipated or perceived threat associated with dental procedures [3]. Unlike fear, which is an immediate reaction to a specific stimulus, anxiety is characterised by anticipation, worry, and heightened vigilance [4].

Dental anxiety often exists at the intersection of mind and physiology. It is shaped by:

- Prior dental experiences and emotional memory.
- Cognitive anticipation and fear conditioning

- Gender-related differences in perception and emotional recall.
- Sensory stimuli associated with dental environments

These factors align with established pathways in the development of dental fear and anxiety. Research has identified five principal pathways through which individuals acquire dental anxiety:

- (1) **Direct conditioning**, where a painful or traumatic dental experience conditions the patient to fear future visits;
- (2) **Vicarious learning**, through which observing or hearing about others' unpleasant dental experiences – for example, a family member's distress – instills fear;
- (3) **Informational threat**, wherein negative information, such as media portrayals or horror stories about dentistry, creates anticipatory anxiety;
- (4) **Verbal threat**, involving intimidating warnings, for example, a parent saying, 'The dentist will hurt you if you don't behave'; and
- (5) **Parental or familial influence**, such as anxious attitudes in parents, can model and transmit fear to children [5].

Each patient may develop their anxiety via a unique combination of these pathways, but the end result is a learned association between dental care and a sense of danger. Over time, this learned fear generalises to the dental environment as a whole, even in the absence of pain. Notably, patients often report that specific sensory cues – the sight of the needle, the sound of the drill, or the smell of clinical antiseptics – immediately evoke anxiety due to these conditioned memories.

Once established, such anxiety leads to a cascade of behavioural consequences: avoidance of appointments, delayed treatment-seeking, reduced cooperation during procedures, heightened pain perception, and diminished adherence to maintenance care. These outcomes predispose individuals to higher periodontal disease risk and reduced treatment acceptance, directly impacting periodontal health and making the condition not merely psychological but inherently clinical [6].

In extreme forms, dental anxiety can manifest as odontophobia (dental phobia), which is recognised in diagnostic manuals (ICD-10 and DSM-5) as a specific phobia. In these cases, the fear is excessive or unreasonable, and the phobic situation is avoided or endured with intense distress, often interfering with the person's normal functioning. [1]

3. Scientific basis of dental anxiety

Physiologically, anxiety activates the sympathetic nervous system, elevates arousal, and lowers pain tolerance thresholds.

3.1 Physiological substrates of dental anxiety

Anxiety begins within the central nervous system. Threat-related perceptions activate the amygdala, which initiates the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system responses, resulting in the following [7]:

- Increased heart rate;
- Muscular tension;
- Heightened vigilance;
- Lowered pain threshold;
- Amplified sensory perception.

This physiological arousal explains why even routine periodontal procedures feel exaggeratedly uncomfortable in anxious patients (see **Table 1**). The sympathetic surge enhances nociceptive sensitivity, meaning that sensations such as probing, ultrasonic vibration, and gingival bleeding feel more threatening than they physiologically are.

Clinically, these responses manifest as:

- Exaggerated flinch responses;
- Defensive movement during instrumentation;
- Difficulty tolerating ultrasonic scaling;
- Increased procedural stress for clinician and patient.

3.2 Behavioural conditioning and anxiety memory

Dental anxiety is reinforced through learning mechanisms. Patients internalise distressing dental encounters as emotional memory. When they re-enter a dental environment, the memory resurfaces, triggering anticipatory fear even before treatment begins.

Physiological system	Response	Clinical relevance in periodontics
Autonomic nervous system	Sympathetic activation	Increased anxiety, restlessness, reduced tolerance
Endocrine response	Cortisol release	Stress, delayed emotional calming
Pain pathway modulation	Lowered pain threshold	Greater perceived pain during scaling/probing
Muscular response	Increased muscle tension	Gagging, difficulty maintaining mouth opening
Cardiovascular changes	Tachycardia, BP elevation	Medical safety consideration during procedures

Table 1.
Physiological responses observed in dentally anxious patients.

Key behavioural mechanisms include [8]:

- **Classical conditioning** → negative experience paired with the dental environment;
- **Operant conditioning** → avoidance is rewarded by temporary relief;
- **Cognitive anticipation** → ‘this will hurt’ thinking;
- **Emotional recall** → previous episodes remembered vividly.

3.3 Neurobiological and psychosocial factors in dental anxiety

While conditioning and past experiences explain much of dental anxiety, intrinsic patient traits also significantly influence its development. Some individuals are inherently more susceptible to intense dental fear due to psychological disposition, genetic vulnerability, or neurobiological sensitivity.

Key intrinsic contributors include:

- **Neuroticism** → A personality trait linked to heightened negative emotionality and threat sensitivity [9].
- **Heritability** → Approximately 30% of dental anxiety is genetically inherited (twin study evidence) [9].
- **Pain sensitivity linkage** → Strong genetic correlation (~ 0.84) between heightened pain perception and dental anxiety [9].
- **Comorbid psychological disorders** → Generalised anxiety, panic disorder, depression, and specific phobias often coexist and intensify dental fear [1].
- **Hyperactive stress-response system** → Overactive amygdala and low stress tolerance observed in high-anxiety individuals [1].
- **Shared vulnerability** → High scores on general anxiety scales reliably predict high dental anxiety (e.g., GAD-7 vs. MDAS correlations) [10].

This synthesis highlights that, for many patients, dental anxiety is not solely situational but reflects a deeper psychological and neurobiological predisposition.

4. Clinical translation and management protocols

Dental anxiety should be approached as a clinical variable, not a psychological afterthought. Integrating anxiety management into periodontal care improves cooperation, procedural comfort, patient trust, and long-term maintenance outcomes.

4.1 Chairside communication and behavioural approach

- **Acknowledge anxiety early:** Brief screening conversations before treatment establish trust.
- **Explain-before-doing:** Patients tolerate procedures better when expectations are clear. This transparency can preempt imaginative fear.
- **Use calm, steady language:** Reassurance reduces sympathetic activation and perceived pain.
- **Build positive memories:** Supportive experiences reduce future anticipatory anxiety.

4.2 Procedural strategies in periodontics

- **Optimise pain control:** Provide adequate anaesthesia when necessary to minimise procedural distress.
- **Gentle, patient-paced technique:** Adopt a gentle probing technique and considerate instrumentation during scaling.
- **Optimise the environment:** Structure treatment into manageable segments for highly apprehensive patients.
- **Maintain a calming clinical environment:** Noise, vibration, and visual stimuli strongly influence perception.
- **Signal and control:** Agree on a ‘stop signal’ (such as raising a hand) that allows the patient to pause the procedure at any time. This restores a sense of control for the patient and can be very empowering.

4.3 Patient support and long-term behavioural conditioning

- **Encourage regular dental visits** to break the avoidance cycle associated with anxiety.
- **Reinforce good oral hygiene behaviours**, as confidence improves when patients feel in control.
- **Adjunct therapies for severely anxious individuals:** Consider anti-anxiety medication, psychological counselling, cognitive-behavioural therapy (CBT), or sedation-supported care when appropriate [1].
- **Techniques such as systematic desensitisation, guided visualisation, or brief interventions**, like having the patient practice relaxation breathing or mindfulness exercises, can complement dental office management.

Incorporating these patient-centred strategies ensures periodontal therapy is not only clinically effective but also emotionally safe, improving acceptance, quality of care, and periodontal stability.

5. Synthesis of evidence on dental anxiety in periodontal practice

From our previously published study [2], which assessed dental anxiety in adult patients undergoing routine scaling and polishing, several key trends emerged. The study revealed a high prevalence of anxiety, particularly among female patients. Apprehension peaked during probing and local anaesthetic administration, and individuals with infrequent dental visits or negative prior experiences reported heightened anxiety levels. These patterns emphasised the roles of gender, emotional recall, and procedural anticipation in shaping the dental anxiety experience.

To reinforce the clinical relevance of these patterns, a curated review of peer-reviewed studies is presented, summarising how dental anxiety manifests, is measured, and impacts periodontal care across diverse populations and settings (see **Table 2**).

Author (Year)	Country	Study population	Anxiety assessment tool	Key findings relevant to periodontics
Ng & Leung [11]	Hong Kong	Cross-sectional survey of 1,000 adults	Dental anxiety (Short Dental Anxiety Inventory) and full-mouth periodontal status (clinical attachment loss, CAL).	High dental anxiety was associated with significantly greater periodontal attachment loss and higher DMFT (decayed/missing/filled teeth). It was concluded that dental anxiety is a risk indicator for poorer periodontal status and lower OHQoL.
Guzeldemir et al. [12]	Turkey	Adults with chronic periodontitis	Visual Analogue Scale	Anxiety correlated with increased pain perception during SRP.
Aragão et al. [13]	Brazil	Systematic review of 11 studies (8 case-control, 3 cross-sectional)	Varying anxiety measures and study designs.	Eight out of eleven studies showed that periodontitis patients had significantly higher anxiety levels than those without periodontitis.
Sreeja et al. [2]	India	Adult dental patients	Questionnaire-based assessment	High prevalence of anxiety; females showed higher anxiety; probing and injections were major triggers.
Bhat et al. [14]	India	Cross-sectional study of 836 army recruits	Anxiety: Corah's Dental Anxiety Scale (DAS) and periodontal health via the Community Periodontal Index (CPI/CPITN).	Dental anxiety was present in approximately 47% of participants and was significantly associated with higher CPITN scores, greater caries experience (DMFS), and more sites with deep periodontal pockets requiring treatment.

Author (Year)	Country	Study population	Anxiety assessment tool	Key findings relevant to periodontics
Lenk et al. [15]	Germany	Cross-sectional survey in dental clinics	-	Dental anxiety strongly predicted periodontitis, correlating with other psychological issues and lower socioeconomic status, emphasising the need for psychological considerations in periodontal care.
Punnyamol et al. [16]	India	Pilot intervention study (n = 10) on periodontal surgery patients	Anxiety measured by Corah's DAS and physiological parameters; Intervention: relaxing music played during periodontal flap surgery	Music therapy significantly reduced anxiety during periodontal procedures, lowering heart rate, blood pressure, and perceived pain. Most patients felt more relaxed post-surgery, supporting music as an effective non-pharmacologic anxiolytic.
Açıkgöz Alparslan [17]	Turkey	Cross-sectional study of 191 dental patients	Modified Dental Anxiety Scale (MDAS) and Dental Fear Scale (DFS); periodontal status evaluated by CPI and the 2017 classification of periodontitis.	Mild dental anxiety was most common, but approximately 24% had moderate to high levels, especially among females. Higher anxiety correlated with worse periodontal health, highlighting the need to manage fear to improve outcomes.
Lenk et al. [18]	Germany	Cross-sectional case-control study comparing 61 patients with severe dental phobia versus 69 age-matched non-anxious dental patients.	Comprehensive oral exams and questionnaires (OHRQoL, life satisfaction) were administered pre-treatment.	Dentally phobic patients exhibited significantly worse periodontal health, higher caries rates, and poorer quality of life, marked by emotional distress and social embarrassment. The study underscores the urgent need for early anxiety interventions in dental care.

Table 2.
Summary of key studies evaluating dental anxiety in periodontal and oral prophylaxis settings.

6. Discussion

Dental anxiety is a prevalent and clinically significant condition that extends beyond a fleeting fear of dental procedures. It forms part of a broader anxiety spectrum linked to mental health, often accompanied by psychological distress and heightened stress responses. These emotional reactions trigger physiological changes, influencing both patient behaviour and biological response to treatment. Dental anxiety is therefore not simply a clinical inconvenience, but a recognised psychological condition with measurable behavioural, physiological, and public-health implications [19]. In fact, severe dental fear (odontophobia) is officially recognised as a specific phobia in psychiatric classification, and is frequently comorbid with other mood and anxiety disorders, such as generalised anxiety, panic disorder, or specific phobias, exacerbating its impact on oral healthcare engagement.

In periodontics, this becomes particularly critical because periodontal stability depends on regular preventive visits, treatment willingness, cooperation, and long-term maintenance. Anxious patients frequently delay or avoid appointments, allowing periodontal disease to progress to more severe stages, creating a self-perpetuating cycle where fear fuels neglect, and neglect worsens disease. Evidence consistently demonstrates that individuals with higher dental anxiety present with poorer periodontal status and compromised treatment outcomes – even when plaque control is adequate [20]. Psychological stressors may, therefore, represent independent risk factors for disease progression by impairing host immune response and wound healing.

Dental anxiety also affects how patients perceive and tolerate treatment. Highly anxious individuals report greater pain during even routine procedures, such as scaling and probing. Psychophysiological, anxiety heightens sympathetic activity, lowers pain thresholds, and amplifies sensory perception – making otherwise minor procedures feel threatening. This pain–anxiety connection is further supported by research indicating a strong genetic correlation between heightened pain sensitivity and dental fear, suggesting that some patients may be biologically predisposed to both [9].

Our findings confirm that anxiety is present even during routine scaling and polishing and is particularly pronounced among females, aligning with global literature showing greater vulnerability among women [21]. This gender-based variation may be influenced by heightened emotional awareness, lower pain tolerance thresholds, and increased memory retention of distressing dental encounters among women. Additionally, sociocultural factors often encourage women to express distress more openly, further amplifying reported anxiety levels. These differences underscore the need for gender-sensitive approaches to anxiety management in periodontal care.

Beyond behaviour and pain, dental anxiety exerts a biological influence. Chronic psychological stress activates the HPA axis, disrupts immune-inflammatory regulation, elevates pro-inflammatory cytokines, and is associated with delayed wound healing and poorer periodontal treatment response [7]. Thus, dental anxiety is not merely emotional; it biologically influences recovery and must be addressed alongside clinical therapy.

7. Conclusion and future perspectives

Dental anxiety in periodontal care is real, prevalent, and clinically consequential. Even routine procedures can provoke significant emotional responses, particularly in female patients. Recognising anxiety as a modifiable clinical factor enhances treatment acceptance, improves the procedural experience, and protects long-term periodontal outcomes.

Future directions should explore physiological monitoring, such as real-time heart rate or cortisol measurements during dental visits, to better understand patient stress levels, as well as tailored behavioural interventions. The development of anxiety-responsive periodontal protocols might include adaptive appointment scheduling. Additionally, there is room for innovation in dental technology with the patient's comfort in mind – devices that are quieter or less invasive could mitigate some sensory triggers of anxiety. Importantly, greater interdisciplinary collaboration between dentistry and mental health professionals can yield new approaches.

When clinicians treat both the tissue and the temperament, dentistry becomes more humane, predictable, and profoundly effective. Embracing this holistic approach will improve not only periodontal health outcomes but also the overall well-being and trust of the patients we serve.

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Conflict of Interest

The authors declare no conflict of interest.

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Chapter 5

War Anxiety and Resource-Holding Potential

Hugues Lagrange

Abstract

Examining why prolonged exposure to war does not lead to a continuous increase in post-traumatic stress disorder (PTSD) among civilian populations, the chapter argues that traumatic stress depends less on the objective intensity of events than on individual sensitivity thresholds shaped by hormonal regulation, cognitive appraisal, and personality traits such as low neuroticism, high openness to experience, or novelty seeking. Drawing on epidemiological data from Ukraine, it shows that, despite repeated shelling, PTSD prevalence remains relatively stable. This resilience is conceptualized through an extended notion of resource-holding potential, encompassing biological regulation, personality dispositions, and social resources.

Keywords: stress, PTSD, resource-holding potential, war, openness to experience

1. Introduction

When faced with danger, everyone feels alarm in the moment, but in some individuals, the body is unable to restore balance, and the hippocampus, the seat of memory, stores bad news as a repository for feelings of unease. When the danger has passed, if its traces are not sufficiently attenuated, the weight of negative experiences accumulates heavily in the hippocampus; traumatic memory increases every day with mundane events, month after month with more serious ones. One of the major aspects of human reactions to danger is that the body does not forget [1]. The body–mind is an accumulator of both good and bad things. While most individuals, due to moderate susceptibility and good resilience, manage to restore balance and can cope with new stressful events under good conditions, for others, stressful pressures do not fade away and lead to traumatic pathologies. As a result, we do not simply react to the problems of the day; the impact of adversity augments. However, one observes relative stability and boundedness of risk for post-traumatic stress disorder (PTSD) in people chronically exposed to aversive events.

The goal of this chapter is to account for the distortion among civilian people facing an enduring war and to identify some of its determinants. We will review the role of event characteristics (e.g., severity of trauma), appraisal of the events, and individual psychic traits.

2. Stressors and stress effects

Psychic trauma emerging after aversive events follows a specific path. Three categories of stressors are usually distinguished. Acute time-limited stressors, either artificial, such as mental arithmetic under constraints, or brief natural stressors related to real-world challenges like public speaking, exams, or performances, form the first type. Severe stressful events, such as the loss of a spouse, a major natural disaster, a deep wound, or an incurable disease, form the second type. Moderate chronic stressors – unexpected delays, deadlines, work constraints – that permeate a person's life form the third type. These stressors trigger a specific response, named stress, understood as the first step in internalizing these adversarial situations, encompassing different psychic and neurophysiological modalities according to the nature of the stressors¹.

In people who have experienced severely stressful events (such as the death of close relatives), the probability of depression is high; however, this response is not systematic. Conversely, acute stress rarely leads to depression or stress traumatic disorder. In addition, an adaptive response is less common in individuals repeatedly exposed to war-like situations (such as those who have experienced recurrent bombings and physical violence). We also know that events, even if they fall into the category of severe stressors, when repeated, act as chronic stressors.

It is difficult to think that the risk for somatic pathologies, such as cancer or diabetes, stems from the subjective assessment of one's own state of mind or mood. Unlike physical injury, wounds, or infections, perceptions and assessments of danger interfere strongly with hormonal, inflammatory, and immune responses. To cope with stressors, the body uses not only an automatic mechanism, namely the secretion of cortisone at the hormonal level, but also active resilience mechanisms carried by neuromodulators. This adaptive process depends on the ability and willingness to reassess dangers that rest on an individual's internal, intangible resources; in other words, dispositions come into play, and so does deliberate behavior.

The word resilience refers, on one hand, to the automatic healing processes that the body implements – in the presence of a skin injury, for example – and, on the other hand, to an intentional process resulting from our emotional and cognitive grasp of danger. Part of the response to stressors stems from resources engaged by the mind, or more precisely, the cortex–hippocampus complex. If we adopt an active stance, such as telling ourselves, “I’m not going to let myself be put-down,” an acknowledgment of adversity – not a denial of harm – can allow for an adaptive reassessment of dangers by the cortex–hippocampus system. The awareness of the consequences of past dangers, stored in the hippocampus, can lead to a modification of the perception of the danger and influence sensitivity. These observations do not close but rather open questions about the determinants and mechanisms of our behavior.

3. Hormonal response to stressors and sensitivity

Acute stressors trigger an immediate reaction of stress, typically manifesting as a fight-or-flight response and resulting in temporary physiological changes such as an increased heart rate, the release of adrenaline, and activation of the

⁶⁸ Moreover, there is often in usage confusion between stressors and their psychological impact.

hypothalamic–pituitary–adrenal (HPA) axis, which departs from balance. Anxiety caused by adversity involves, as stated, many neurotransmitters in addition to hormones, particularly between the hippocampus and the hypothalamus, but hormonal responses play an essential role in the development of mental disorders, and the following analysis will be limited to hormonal dynamics.

In response to the perception of a potentially stressful event by the amygdala, three hormones – corticotropin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH), and cortisol (CORT) – are produced. This operates through an increased hormone concentration in the HPA axis. The first level of response to a brief external stressor is a surge of CRH, leading to an increase in ACTH concentration, followed by cortisol in the HPA axis. After stimulation by a moderate stressor, corticotropin and cortisol production stabilize, as shown in **Figure 1**. This corresponds to the homeostatic functioning of the hormonal response. The initial production of CRH depends on a sensitivity threshold that correlates with the individual's overall vulnerability (which itself depends on genetic factors and past experiences). During this process, the “emotional component” of the information is separated from the “factual component,” and the state of stress is reduced. This relative decoupling results from the autonomy of the processing of external afferents by the cortex and limbic brain, particularly the components of the immediate hormonal response and the memorization of past experiences consolidated in the hippocampus. The elevation in the sensitivity threshold is inversely proportional to the variation in cortisol concentration caused by stress. This inverse relationship reflects the fact that, for the same aversive stimulus, the flow of cortisol from the adrenal cortex causes a lowering of the response threshold, increasing the sensitivity of the amygdala/hippocampus complex, and thus reinforces the traumatic event memory. However, the intensity of this relationship is modulated by the sensitivity to events, which depends on psychological and social parameters.

The neurophysiological sensitivity to violent events, generating intrusive and upsetting memories, sometimes more potent than the events themselves, is correlated to pathological states – anxiety, depression, and specifically PTSD. The hormonal cascades ensuing an event are determined by the gap between the intensity

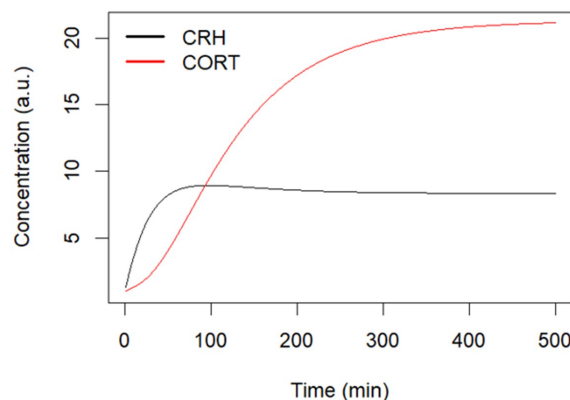


Figure 1.
Time dynamics of the corticotropin-releasing hormone (CRH) and cortisol (CORT) concentrations without stress. A.U. means arbitrary units. Author's graph using R code according to a modified model by Gonzalez-Heydrich et al. [2].

of the external stressor and individual sensitivity. Thus, the sensitivity threshold driving the HPA hormonal response implies that the aversive events' perceived intensity is higher than a threshold specific to the individual².

4. Sensitivity and personality: Big five traits

To overcome negative events, there are two major parameters: the speed of elimination of transient stress and the positive appraisal of past reactions to aversive events. These parameters are at the heart of the psycho-social dynamic.

There is a latent period between an aversive event and the neuro-hormonal response, during which people evaluate their past behavior. Some individuals are strengthened by the experience of dangers, whereas others are destabilized and become more sensitive.

First, the kindling hypothesis suggests that “repeated or prolonged exposure to stressors will make people more sensitive to stressful events because these experiences lead to neurobiological and cognitive changes that reduce one's threshold for perceiving stress [3].” It amounts to lowering the sensitivity threshold (σ in the model in the appendix). Second, the inoculation hypothesis asserts that chronic stressors “may make people less sensitive ... because they habituate to stressors or, alternatively, gain experience with coping [3]”, raising the sensitivity threshold. Kindling and inoculation hypotheses are not mutually exclusive; both assume that individual stress responses arise from cumulative exposure to stressors. We will focus here on the conditions of positive responses to adversities.

The individual sensitivity, which has been considered a crucial setpoint for psychic unbalance, depends on innate characteristics, partly inherited and partly acquired. Two aspects of resilience must be taken into consideration: speed of recovery and stressor appraisals.

5. Speed recovery

Using the Big-Five scale, several researchers have shown that people high on the neuroticism scale tend to perceive events as very stressful and uncontrollable, whereas those high on conscientiousness, extraversion, and openness to experience tend to perceive such events as within their control. Openness to experience is a general dimension, seen in “vivid fantasy, artistic sensitivity, depth of feeling, behavioral flexibility, intellectual curiosity, and unconventional attitudes [4].” Several researchers show that people suffering from PTSD generally have a low score on the scale of openness to experience. A high level of openness implies cognitive flexibility, allowing information that causes emotional destabilization to be assimilated more quickly. Conversely, low openness is characteristic of a rigid cognitive system and a slow management of imbalance (see parameter τ in the model in the appendix, Eq.(6)).

⁷⁰ Formally, as developed in appendix, the stress felt is a function of $(S_t - \sigma_t)$, where S_t indicates the strength of the external stressor which is experienced only if higher than the individual sensitivity threshold σ_t at time t .

6. Events positive appraisal

Broad individual differences in personality also have robust associations with stressor appraisals. Savic et al. [5] point out that “the speed at which an individual recovers from a stressing situation is linked to a general propensity to engage in new experiences and the ability to learn.” The accumulation of negative memories depends on the sensitivity threshold, that is, the minimum external stimulus capable of causing an increase in HPA axis activity. If a person has a low threshold for triggering stress hormones (CRH, ACTH, and cortisol), the release of these hormones will consolidate the memory of many events as negative experiences in the hippocampus. Individuals who have a negative subjective assessment of their past reactions to danger, in whom the ratio of positive to negative perceptions is less than one, see their threshold of sensitivity decrease and become more fearful as exposure continues. Conversely, people who enjoy novelty are likely to cope better with stressful situations and therefore evaluate their response as successful. An inverse relation has been observed between cortisol concentration and negative event appraisal, which supports the link modeled by Eq. (7) between the sensitivity threshold σ and the appraisal of past events [6].

7. Cloninger framework for resilience

A very similar interpretation could be based on a slightly different personality framework [7]. The framework defined by Cloninger’s *Temperament and Character Inventory* is especially appropriate for understanding the risk of trauma associated with war. Cloninger defines a main dimension, called harm avoidance, which is closely related to the first dimension of the classical personality inventory crafted by Eysenck [8]. Namely, the difficulty of recovering from an aversive event is correlated with harm avoidance. “Numerous studies have shown that subjects with current mood or anxiety disorders typically have high scores on the harm avoidance scale A person high on the harm avoidance scale is very likely to have a high neuroticism score, as evidenced by the high correlation between these two traits ($r = 0.75$) [9].” The ability to cope with danger is also correlated with Cloninger’s novelty seeking and positive learning, a dimension similar to openness in the Big-Five. A high score is directly predictive of a positive evaluation of past experiences where coping has been felt successful (see Eq. (7) in the model in the Appendix).

A note of caution is nevertheless needed. We must not jump too quickly to the conclusion that these personality traits are only proxies for cognitive abilities or level of education. Research shows that novelty seeking, on one hand, and harm avoidance, on the other, while correlated to education with the right sign, are not significantly linked to it (see **Table 1** below).

The study shows that persistence is related to education. This might contribute to resilience, which manifests in the relative boundedness of PTSD prevalence in adverse contexts.

Resilience, under the dual aspect of physiological behavior and memory, is not only or mainly a by-product of cognitive attitudes. Low harm avoidance and high novelty seeking, which are related to a positive response to acute stressors, are nevertheless important assets in the context of war.

Correlations	Novelty seeking	Harm avoidance	Reward dependance	Persistence
Age	-0.33*	0.15	-0.09	-0.002
Education	0.08	-0.05	0.13	0.17

Source: Study by Tuominen [9].

*Significance: 0.001.

Table 1.

Correlations of Cloninger temperamental dimensions with age and education³.

In summary, the patterns of stress appraisal in adaptive ways partially account for the negative health outcomes associated with neuroticism and low openness to experience traits of the Big-Five, or to harm avoidance and novelty seeking in Cloninger terms. Thus, if the effects of physical danger and violence are perceived as controllable, it can result in a sense of personal meaning, mastery, and other positive consequences in the short and long term. This supports a transactional perspective on the effects of attitudes and context.

8. Ukraine war: Beyond psychic traits, social resources

The situation of high-intensity war in Ukraine has led authorities to encourage epidemiological studies aiming to assess the moral and mental health of the civilian population. Nearly 20 epidemiological surveys were conducted in the years immediately preceding and following the invasion of 2022. This series of epidemiological surveys provides a perspective on the temporal evolution of psychological damage. It appears that despite the protracted war, PTSD among the civilian population is not exploding. Epidemiological surveys show a correlation between the intensity of bombing and the prevalence of traumatic stress disorder observed at any given time, but when examining the series, there is no upward trend in its prevalence across time. The limited evolution of the prevalence level of PTSD in Ukraine suggests that, in a large fraction of the population, a process of attenuation of the trauma elicited by the shelling, destruction, and casualties has gained momentum (see **Figure 2** below).

Indeed, the literature on PTSD has shown that there is a greater prevalence of PTSD following exposure to “interpersonal violence” as compared to “accidents,” suggesting that “the former are more potent stressors and accordingly increase one’s risk by providing an increased ‘dosage’ of trauma [10].” In contrast to interpersonal violence, which may reflect socioeconomic or even genetic predictors of event exposure, war adversities in the civilian population are, to a certain extent, like random accidents, except that they recur over a short period.

Osokina et al. [11], comparing war experiences and risks of traumatic stress disorder, anxiety, and depression among adolescents living in the peaceful Kirovograd region with those residing in Donetsk, where the conflict has raged since the 2014 Russian invasion, indicate that the prevalence of traumatic stress disorder

⁷² ‘Structural neuroimaging studies pertaining the regional specificity of brain-temperament relationships demonstrated positive correlation between Novelty Seeking and gray matter volume in frontal and posterior cingulate regions as well as between Harm Avoidance or anxiety related traits and reduced volumes of whole brain, orbitofrontal, occipital, parietal and left anterior prefrontal cortex [17].’

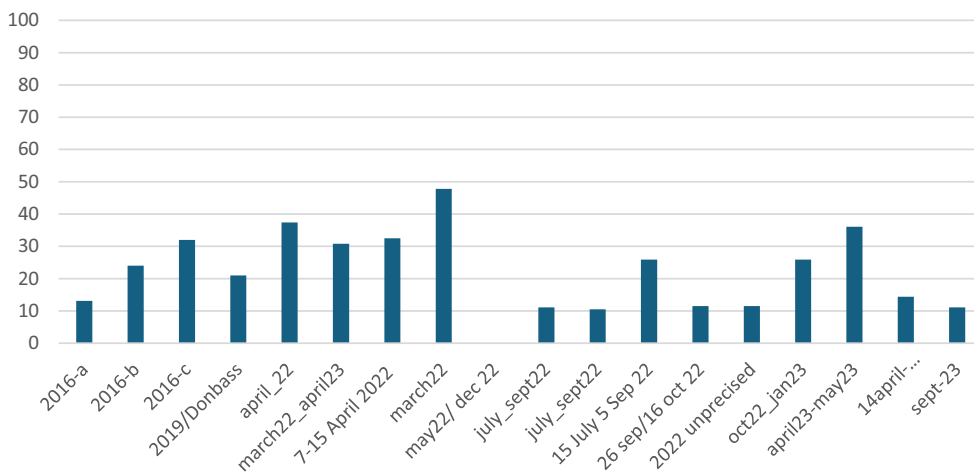


Figure 2.
 Prevalence of post-traumatic stress disorder in 2016–19 2022–23 in Ukraine. Source: Compilation by the author, based on available surveys. The x-axis shows the data collection period. A survey conducted between May and December 2022 was excluded for reasons of reliability.

among young people in the latter is significantly higher. Repetition of events, particularly bombing, may exacerbate the disorders and have a cumulative impact. This was expected; however, the study shows that many young people exposed to hostilities appear to have adapted psychically and behaviorally to the risks of war. Consequently, variations in the prevalence of these disorders do not correspond precisely to the geographical distribution of war pressure.

Displaced people took steps to respond to the threat by going to live with relatives who were hostile to the aggressors and may have found some comfort in this way. In the same manner, over time, most people have been able to distance themselves from stressful events – sirens, destruction, injuries, and even deaths – and to elevate the threshold for triggering harmful neurophysiological reactions. If, among the elderly, we observe a lowering of the stress threshold that triggers a disruption of homeostasis, and therefore an increased risk of pathology, among the majority of people, good dispositions unconsciously raise the threshold of hormonal reactions, limiting the overreactions that lead to pathologies. This automatic mechanism is supplemented by a subjective propensity to put danger in perspective, particularly conspicuous in a context where injuries and deaths are recurring events faced by the collectivity.

That repeated severe stressful events are associated with a moderate risk of PTSD may seem counterintuitive. However, this is a point of consensus in psychiatric literature, whereas even moderate, chronic stressors are known to lead to a high level of pathologies. The traumatic stress disorder does not reflect the intensity of direct physical pressures; the conditions that lead to traumatic stress are not to be found mainly in the nature of the events themselves. The model used, inspired by Gonzalez-Heydrich et al. [2] and Savic et al. [5], shows that, in the absence of a conscious moderating action, the rate of recurrence of stressors going faster than that of returning to homeostasis makes the stress load too heavy and overwhelming. After a stressful event, the threshold may increase or decrease according to the short-term event elimination speed and the coping attitude

defined by the ratio of positively to negatively perceived past responses. The sensitivity dynamics linking past events appraisal and human recovery competences remain to be empirically verified with data, including hormonal and psychological measures that integrate responses at different levels. However, tests on the psychological trait effects already suggest the appropriateness of this framework [6].

9. Resource-holding potential and ability to overcome stress

“Risk factors for PTSD include a family history of psychopathology, cognitive factors such as lower IQ, childhood adversity, preexisting avoidant personality or behavioral problems, and poor social support [10].” The ability to avoid mental imbalance, which is neither purely a fighting nor cognitive one but articulates emotion and reason, might be summarized by the concept of resource holding power or potential (RHP). In animal ethology, the traits typically considered to determine RHP include body mass and size. However, Price et al. [12] explain, in substance, that beyond an animal’s physical capacity to win a fight for vital resources, specific psychic traits such as boldness, aggressiveness, and motivation significantly influence the outcome by affecting the willingness to fight. A bolder, more motivated animal might win despite being smaller. An owner with prior possession, albeit fragile, might fight harder against an intruder: these attitudes, considered as a configuration of traits or resource potential, are not distributed at random in a population.

Resource potential is the basis of common behavior that individuals in groups and society at large use to navigate the social hierarchy through a constant, low-noise process of escalation/de-escalation balance, to find the more advantageous relative situation. However, the resource potential accumulated also provides a framework within which to understand the processes involved in experiencing, coping with, and becoming resilient to chronic and traumatic stress. The strategies associated with resource potential do not always involve, in modern contexts, a propensity to escalate but at least a propensity not to give up – perseverance and tenacity.

These basic premises have been supported by empirical work. Men in contemporary societies rarely face the agonistic power of predators; instead, interactions with conspecifics are shaped by competition for prestige as the main means of constructing and maintaining social hierarchies. Dealing with these issues requires a response combining three levels: cortical, limbic, and instinctive [12, 13]. Price asserts that modern competition for dominance and prestige in complex societies has not prevented escalation and de-escalation behaviors from surviving the transition from agonistic competition to social prestige competition. In the same manner, overcoming stress still implies coordination between rational, emotional, and instinctive levels in ordinary life as in wartime. In peacetime, as said, social life exposes individuals to three types of stressors: acute brief, severe, and chronic; war as well, subjects the civilian population to severe repeated stressors that, surprisingly, have effects partly similar to ordinary life chronic stressors. In both cases, there are hormonal responses that are not so different and whose magnitude depends on resource potential – a latent capacity to cope with adversities and danger.

People who have a low level of neuroticism and high openness to experience (Big Five), or low harm avoidance and high novelty seeking (TCI), have high social resilience potential, which can be considered components of Price’s resource-holding potential. The attitudes that govern speedy recovery and transition from a negative assessment of past responses to a positive assessment depend on these intangible, immaterial resources (summarized in columns 2 and 3 of **Table 2**).

A notion of resource potential, informed by personality traits, can be built by analogy to Price’s RHP [13]. It requires an adaptation of the major social processes – escalation and de-escalation – grounding social hierarchies. As with escalation and de-escalation, it relies on triune brain functioning. The connections between the cortical and limbic/reptilian levels are also evident in the behavior adopted in response to adversities. Decisions crucial for resilience, which govern the shift from a negative to a positive assessment of past responses, depend less on the combative capacity covered by the ethological pristine notion than on personality openness. Neurobiology shows that somatic responses – hormone concentrations and, consequently, sensitivity thresholds – interact with cortico-limbic determinations in a bi-directional way. Glucocorticoids are known to enhance memory storage; thus, cortisol flowing back to the hippocampus, crossing the blood–brain barrier, reinforces the storage of bad memories and triggers symptoms constitutive of PTSD. Conversely, cortex–hippocampal taming of past adversities reduces sensitivity in light of adaptive responses and contributes to preventing a surge in anxiety, post-traumatic stress, and depression.

This conception is akin to the *Conservation of Resources* theory, suggesting that human behavior tends to minimize resource loss. “For example, vigor, hope, and self-efficacy are located within the individual and are key, as they provide the energy and motivation to seek and maintain external resources such as stable employment and supportive relationships.” Two principles underlie this theory. Principle 1 states that resource loss is disproportionately more salient than resource gain in both degree and speed of impact. Principle 2 states that people must invest resources to protect against resource loss, recover from losses, and gain resources.... Similarly, psychological distress – including both probable PTSD and probable depression – is predicted by resource loss [14]. These resources determine the pugnacity of the members of a population, or rather of a fraction of it, whose size is decisive to the course of events [15, 16].

Personality configuration defining	High ressource holding potential harm avoidance: low novelty seeking: high perseverance: high	Low resource holding potential harm avoidance: high novelty seeking: low perseverance: low
Brain levels: Type of behavior associated		
Rational (cortex)	Stubbornness, boldness	Escape, rollback
Emotional (limbic system)	Low fear, elevated mood	High fear, anxiodepression /PTSD
Reptilian (basal ganglia)	Agressive	Passive

Source: Author’s, inspired by Price [13].

Table 2.
Types of behavior in front of aversive events according to resource-holding potential.

10. Conclusion

When faced with the adversities of war, civilians are not expected to fight directly, but it is crucial to avoid a generalization of anxiety leading to a high prevalence of depression or PTSD. The mediator of this process is the building of a structural resilience capacity. As defined above, the resource-holding potential is the basis that individuals, in groups and society at large, mobilize to navigate the war circumstances. This resource potential provides, as such, a framework within which to understand the mechanisms involved in appraisal, coping with, and becoming resilient to chronic traumatic stressors. This potential for action seen in the Ukrainian population is fueled by the sense of political legitimacy of Ukrainian resistance to the invasion. To enhance this potential in the face of the repeated adversities of war is therefore an important sociopolitical goal.

If the population's mood is likely to be influenced by political leadership and collective cohesion, this translates into mental health only under specific conditions. The sensitivity threshold is not an opinion; it is a behavioral characteristic related to individual resource potential, evolving slowly with the experience accumulated. The development made above suggests that the ability to maintain sensitivity to adversities under a threshold in a large majority of the population depends on the relative success of the military action (reducing shelling). Thus, despite the accumulation of direct and indirect injuries inflicted on the civilian population, even though the body, in general, does not forget, this process can explain the limited prevalence of PTSD and the absence of a trend.

Appendix A. A model for developing individual responses to stressors

The first models of response to stressors were built “to accurately simulate the timing, magnitude and decay of the ACTH and cortisol concentration peaks resulting from the *ovine*-CRH-stimulation test, acting as a stressor in normal and hypercortisolemic patients (Gonzalez-Heydrich et al. [2])”. The model developed below to account for that is inspired by Gonzalez-Heydrich et al. [2].⁴ and Savic et al. [5].

The hormonal flow of corticotropin (CRH), adrenocorticotrophic hormone (ACTH), and cortisol (CORT) in the HPA axis may be described by the following three differential equations:

$$d\text{CRH}/dt = F_t \{1 - \eta [\text{CORT}/(k_d + \text{CORT})]\} - k_1.\text{CRH} \quad (1)$$

$$d\text{ACTH}/dt = k_1.\text{CRH} - k_2.\text{ACTH} \quad (2)$$

$$d\text{CORT}/dt = k_2.\text{ACTH} - k_3.\text{CORT} \quad (3)$$

where k_d is the dissociation constant for the glucocorticoid-II receptors, η represents the magnitude of the CRH inhibition by the cortisol feedback flow [0,1].

k_1 , k_2 , and k_3 are positive constants.

⁷⁶ n Gonzalez-Heydrich's model, the negative feedback $-\eta [\text{CORT}/(k_d + \text{CORT})]$ – applies to the ACTH production. The consequences are essentially the same when applied to CRH.

F_t represents HPA stimulation, typically initiated by an aversive event whose intensity is higher than a threshold σ_t , specific to the individual:

$$F_t = k_c^0 \cdot \exp(S_t - \sigma_t) \quad (4)$$

with S_t as a measure of an external stressor, which is experienced only in comparison with the individual sensitivity threshold σ_t at time t .

Eq. (1) shows the impact of the stressor F_t and the CORT concentration, through the dissociation factor k_d , on the CRH production; Eqs. (2) and (3) describe the ACTH and cortisol production. In this process, cortisol's main effect is to inhibit CRH via glucocorticoid-II receptors in the hypothalamus.

The variation of stress sensitivity is inversely correlated with the variation of cortisol concentration; thus, Savic et al. [5] suggest expressing it with one equation:

$$\Delta\sigma_t = -k_4 \cdot \Delta\text{CORT} \quad (5)$$

where $\Delta\sigma_t$ represents the change of σ_t after the action of the external stressor, k_4 is a positive constant.

The memory system and the hormonal system are connected in this way. Thus, "each stressful experience is marked by a change in cortisol concentration, which helps it to be memorized [2]."

This inverse relationship between the variation in cortisol concentration (ΔCORT) and that of the reaction threshold ($\Delta\sigma_t$) reflects a process through which, for the same stimulus, the positive feedback of cortisol from the adrenal cortex will cause a lowering of the threshold (σ), leading to increased sensitivity to stress but also to a reinforcement of the traumatic event in the memory (amygdala/hippocampus).

Without an external stressor episode, the CRH and cortisol production stabilize, as shown in **Figure 2** above. By the same token, in the absence of a strong perceived stress ($S_e - \sigma_0 \leq 0$, where σ_0 is the initial personal threshold under which a hormonal response is triggered by an external stressor S_e , cortisol concentration stabilizes due to a retroactive inhibitory action.

In the presence of a strong external stressor, $S_e > \sigma_0$, there is an attenuation process, and the stress decline following usually an exponential law:

$$S_t = (S_e - \sigma_0) \cdot \exp(-t/\tau) \quad (6)$$

where τ defines the duration for recovery.

The individual sensitivity threshold σ_t depends on previous stressful experiences. After a stressful event, the threshold may increase or decrease according to the event's strength and the coping process defined by the ratio of positively to negatively perceived past responses. For the sensitivity current level, we have adopted the Savic equations with a modification:

$$\sigma_t = \sigma_0 + \Delta\sigma_t \cdot \exp(-t/\tau) + k_5 \cdot |\Delta\sigma_t| \cdot \ln(N_t^+ / N_t^-) \quad (7)$$

where N^+ is the number of positively estimated reactions in one's life experience, N^- is the number of negatively estimated reactions, and k_5 is a constant greater than 0.

According to the idea that adaptive coping raises the sensitivity threshold, we have written $|\Delta\sigma_t|$ instead of $\Delta\sigma_t$ for the last term in Eq. (7), which implies that this adaptive coping increases the value of σ_t . Over time, there is both an erosion of the power of stressors and, to varying degrees depending on the individual, a "healing" process, the speed of which is described by the factor τ in Eq. (7), and "coping,"

which is represented by a weighting of positive and negative reactions in the hippocampus with the term $\ln(N_t^+/N_t^-)$.

R code for simulation is available from the author.

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Conflict of Interest

The author declares no conflict of interest.

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Chapter 6

Anxiety and Neuroinflammation

Carlos M. Contreras and Ana G. Gutiérrez-García

Abstract

Diverse threatening stimuli can give rise to stress, an autonomous response that is usually accompanied adaptively by anxiety. Chronic stress, however, can transform this adaptive process into pathological anxiety, triggering several disorders. Basic research has attempted to study these pathological processes using various animal models, including predator exposure, alarm pheromones as stressors, conditioned stimuli, and social buffering. These models have allowed researchers to establish that the neurobiological basis of anxiety and its deleterious consequences on brain function occur through neuroinflammation processes. Treatments for anxiety continue to rely on anxiolytic drugs with γ -aminobutyric acid-ergic actions, which have sedative and addictive effects. It has not been proven that anxiety is a consequence of a decrease in GABAergic activity, and a different approach is necessary. Current research has shown that neuroinflammation is among the pathophysiological bases of anxiety and other psychopathological processes, prompting the search for various treatments with antiinflammatory properties that act on microglia and cytokines.

Keywords: anxiety, animal models, anxiolytic drugs, neuroinflammation, stress

1. Introduction

Stress is produced by threatening, unexpected, or surprising events that elicit physiological and behavioral responses (allostasis) directed at coping with the situation. This response is regulated by epinephrine/adrenaline, cortisol, and cytokines, with the participation of the amygdala, hippocampus, and hypothalamic–pituitary–adrenal (HPA) axis. However, in situations of prolonged stress or a failure to cope with the situation, stress overload occurs, which can lead to pathological conditions [1–3], such as pathological anxiety.

Early after awakening, the hypothalamic–pituitary–adrenal axis promotes the delivery of glucocorticoids, particularly cortisol, in an ancient adaptive process that prepares the organism to support thirst and hunger by liquid retention and an increase in metabolic rate. Activation of the HPA axis and glucocorticoid release also prepare the individual to cope with threatening situations [4]. However, excess glucocorticoids can damage neural tissue [5] and may exert a negative effect on other organs and systems [6], giving rise to pathological anxiety.

During the day, cortisol (corticosterone) is released in the presence of threatening situations by many vertebrate species [7–10]. In situations of chronic stress, adaptive

anxiety surpasses certain limits, causing structural degeneration and impairments in the function of the hippocampus and prefrontal cortex (PFC) and their connections, which may lead to the occurrence of other neuropsychiatric diseases [11]. For example, allostatic load after chronic stress in a model of long-term exposure to predator odor produces clear signs of anxiety, abnormal behaviors (e.g., alcohol preference), and changes in hypothalamic function [12].

There are individual differences in the response to threatening situations. Some individuals are resilient to stress and develop only adaptive anxiety, whereas others are more vulnerable to stress and develop pathological anxiety. Among many other cerebral nuclei, the insula seems to have a relevant role in anxiety, since the blockade of corticosteroid receptors with mifepristone in this region reduces anxiety signs in animal models [13]. In another case, the early activation of the habenula–interpeduncular system by stress produces hyperactivation in this circuit and anxiety susceptibility in adulthood [14].

A high sensitivity to stress is related to a low density of astrocytic glucocorticoid receptors in the medial prefrontal cortex (mPFC) [15], and a reduction in the expression of glutamate decarboxylase and other enzymatic substrates in the PFC affects the excitation/inhibition (E/I) balance in the dexamethasone model of anxiety/depression [16]. In a long-term follow-up study, it was demonstrated that allostatic load may predict the development of anxiety/depression in about 4% of individuals [17], and from an anatomical point of view, in anxious children, the bilateral size of the amygdala is higher than in a healthy control group [18].

The role of neurotrophins is illustrated by the fact that, in stress-vulnerable rats, the basal levels of BDNF in the mPFC infralimbic and prelimbic (IL-PL) regions were markedly lower than in the stress-resistant rats [19]. Also, a low corticosteroid-binding concentration and low binding affinity of receptors lead to stress sensitivity, chronic fatigue, and pain. Whereas, in the hypercortisolemic case, the high cortisol plasma concentrations are related to hypertension and anxiety [20].

The present chapter reviews the neurobiology of anxiety and discusses the processes involved in the development of pathological anxiety. We consider that most medications prescribed for diverse anxiety manifestations rely on γ -aminobutyric acid (GABA) receptor activity, which produces sedative effects. However, deficiencies in GABA activity have not been demonstrated to be the basis of anxiety, and such GABAergic actions are only a mechanism of action for such groups of drugs. The recognition of neuroinflammatory processes appears to provide a better explanation for pathophysiological anxiety. This chapter concludes with our reflections on other possible treatments for anxiety.

2. Neurobiology

Distinguishing between fear and anxiety is necessary. Fear is a part of anxiety, suggesting the continuity of brain circuits that are involved. The amygdala complex is a brain region involved in the regulation, acquisition, storage, and expression of fear [21], and changes in amygdala function are accompanied by changes in other anatomically and functionally related structures. For example, stress exposure impacts hippocampal function [22], which participates in emotional processing along with corticolimbic circuits.

In rats, the mPFC is composed of a dorsal region (the cingulate cortex) and two ventral regions, the PL and IL cortices, that differentially and selectively participate in fear regulation [23], among many other functions. The PL and IL regulate amygdala activity, exerting modulatory actions on the expression of fear [24]. The IL participates in the extinction process [25], whereas the PL participates in fear acquisition [26]. Additionally, corticolimbic structures comprise other forebrain connections.

Anatomical and reciprocal connections between the amygdala and the lateral septal nucleus exert reciprocal inhibitory actions on each other and their neuronal firing [27]. A single session of stress exposure reduces neuronal activity in the lateral septal nucleus [28]. An increase in the neuronal firing rate in the amygdala is related to fear and anxiety. An increase in neuronal firing in the lateral septal nucleus may be related to pleasure, thus possibly explaining the antagonistic effect of fear on hedonic behavior and vice versa, and possibly stress/anxiety resilience and allostatic load.

In humans, functional magnetic resonance imaging studies demonstrate that activation of the anterior cingulate cortex is related to lower social anxiety, likely by inhibiting the amygdala [29]. It seems clear that the dysregulation of corticolimbic connections is involved in the development of anxiety.

3. Neurotrophic factors and microglia

Plasticity is regulated by neurotrophic factors. In an analogy between peripheral macrophages and microglia, the so-called M1–M2 phenotypes polarization, as a reaction to the presence of LPS or IFN- γ , or by IL-4/IL-13, produces the delivery of proinflammatory cytokines (IL-1 α , IL-1 β , IL-6, IL-12, IL-23, TNF- α) for the resolution of inflammation and tissue repair [30]. In contrast, the brain content of brain-derived neurotrophic factor (BDNF) increases after the administration of anxiolytic drugs [31], giving rise to the promotion of neurogenesis [32], while IL-4 drives microglia [33].

Hippocampal synaptogenesis may be a determining factor in the development of resilience to stress [34]. Microglia adopt at least four forms (ramified, primed, reactive, and amoeboid); such histological patterns are modulated by proinflammatory cytokines in response to several agents producing neuroinflammation, making microglia a good target for pharmacological treatments [35], since M1 and M2 microglia regulate inflammation, synaptic plasticity, neural network formation, pruning activity, removal of apoptotic cells, and pathogens in cerebral nuclei related to emotional behavior regulation [36]. Microglia and BDNF contribute to neural tissue maintenance in two possibilities. Parainflammation is considered an adaptive process and consists of microglial recruitment, changes in cytokine signaling between neurons and microglia, and microglia-mediated neuronal remodeling. This condition is distinguished from a true neuroinflammation process, in which high levels of proinflammatory cytokines, microglia and peripheral macrophage activation, tissue damage, and other anomalies give rise to a disease [37].

The efficacy of successful behavioral changes when coping with threatening situations may be considered a consequence of the actions of neurotrophic factors that influence cerebral circuits involved in the regulation of mood. In fact, in rodents subjected to chronic stress models, the expression and release of BDNF and dendritic

density are altered in the hippocampus, mPFC, nucleus accumbens, lateral habenula, amygdala, and bed nucleus of the stria terminalis; these changes are reversed by ketamine [38].

In the chronic inflammatory disease psoriasis, BDNF plasma levels are lower than in healthy controls [39], but in fibromyalgia, BDNF levels are higher than in healthy controls [40]. At least in women, the perception of stress is modulated by inflammatory cytokines related to BDNF methylation processes [41]. In this sense, it is relevant that BDNF also seems to participate in cognitive functioning [42].

Chronic stress produces overactivity of NMDA receptors that dysregulates calcium signaling, leading to decreased BDNF activity, causing disturbances in neuronal function, and resulting in behavioral alterations [43]. In depressed patients, a single dose of ketamine produces a long-lasting increase in BDNF content in the PFC, dentate gyrus, CA1 and CA3, while glial fibrillary acidic protein (GFAP) increases in the PFC and striatum, in parallel with clinical recovery [44]. On the contrary, the cortisol model of depression produces a low level of BDNF in the hippocampus, and hyperactive neuronal autophagy is observed [45].

4. Animal models

A common failure when exploring anxiety processes and anxiolytic actions is that the animals that are being studied are healthy. In fact, better results may be obtained in animals that have been previously stressed using several methods and procedures. When employing any experimental design, only one symptom of a disease state is usually explored, such as changes in locomotion in various specially designed apparatuses. When addressing a complex behavior, it is often better to use a complete battery of tests, including the burying behavior test [46] and the elevated plus maze [47], to assess signs of anxiety. Lastly, to fully explore the neurobiology of anxiety, electrophysiological studies, such as those employing methodologies to examine the responsivity of limbic structures [48], and neurochemical techniques are essential.

5. Experimental models

Chemosignals and pheromones should also be considered, especially those that signal danger. Exposure to predator scents inhibits the prey's nondefensive activities (e.g., foraging, feeding, and grooming), and the prey avoids places impregnated with them. This is accompanied by endocrine changes [49]. Some pheromones activate the olfactory system and establish allostatic reactions, such as the avoidance of places impregnated with an alarm pheromone [50]. If exposure to alarm pheromones is unavoidable or prolonged, an individual's stress/anxiety resilience capability may be compromised, resulting in allostatic load, represented by signs of high anxiety and hopelessness [51, 52].

Anxiety may be produced by long-term exposure to threatening situations without the possibility of escape. In a model of posttraumatic stress disorder, rats are repeatedly exposed to cat odors. After several sessions, these animals exhibit high levels of fear and stress [53]. A variation of this model is psychosocial stress caused by exposure to predators. When rats are immobilized and have no opportunities to

escape, they are exposed to a cat for several minutes, after which they develop chronic social instability lasting several days and strong signs of anxiety, including exaggerated startle responses, disproportionate reactions to other acute stressors, and cognitive impairment [54].

The forced swim test [55, 56] was originally designed to test the potency of antidepressants. In this test, rodents are introduced into a pool, and the rodent initially displays strong struggling activity, apparently searching for an exit, but after a while adopts an immobile posture and maintains itself floating. This behavior is classified as immobility, which is reduced when animals are pretreated with antidepressant drugs. However, the immobility in the forced swim test is also considered an adaptive response [57], and its actions as a stressor have been documented. A single session of forced swimming produces a decrease in the extracellular content of GABA in the hippocampus [58] and, like other stressors, increases the plasma and hippocampal levels of inflammatory cytokines – changes that are reversed by fluoxetine [59]. It is noticeable that the findings are similar to those observed in other models producing anxiety- and depression-like behavior.

6. Social buffering

Social buffering is a phenomenon whereby a stressful situation experienced in the presence of mates is associated with a better ability to cope with the challenge [60]. These actions appear to be mediated by olfactory cues [61]. After a chronic stress protocol in isolated rats, basal levels of plasma corticosterone decrease, deficiencies in long-term memory occur, BDNF gene expression decreases, and changes in hippocampal function are observed relative to control rats that live with other rats [62]. In rats tested in groups, social contact mitigates the effects of chronic stress through heightened dopamine activity in the basolateral amygdala [63]. The perception and regulation of fear are governed by basolateral amygdala-mPFC circuitry [64], with the involvement of prefrontal oxytocin [65] and the IL subregion of the mPFC [66].

7. Conditioned stimuli

Animal models of posttraumatic stress disorder are accepted as a valid means to understand anxiety [67, 68]. In laboratory animal studies, rats that fail to escape from foot shocks exhibit an increase in metabolic activity in the lateral septum and habenula [69]. In stress-/anxiety-resistant rats, BDNF expression is upregulated in the ventral hippocampus [70]. In a posttraumatic stress disorder animal model, stress/anxiety-resilient individuals express higher metabolism in the right anterior insular region and adjacent prefrontal and striatal areas [71]. In stress-/anxiety-resilient rats, basolateral amygdala dendrites are more densely packed and shorter than neurons in stress-sensitive or non-exposed control animals [72].

In summary, an adaptive process of anxiety provides the opportunity to cope with different aversive or threatening stimuli. In an allostatic process, the participation of the HPA axis and the release of glucocorticoids produce a general reaction in brain function, involving GABA, glutamate, and neurotrophic factors, successfully modifying the E/I balance. However, due to many factors, including

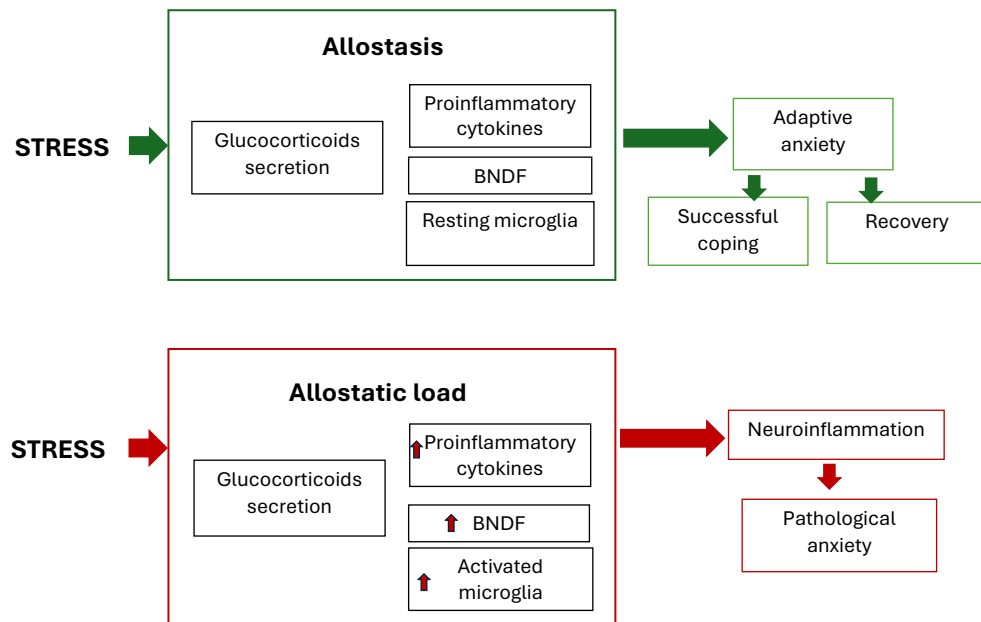


Figure 1. Diagram illustrating the possible processes involved in the development of anxiety as an adaptive response (top panel) and pathological anxiety (bottom panel). Both processes involve the same proinflammatory and antiinflammatory systems and the same brain structures (see text). The difference lies in the fact that in pathological anxiety, these processes are dysregulated.

previous experiences and the quality and duration of the threatening or emergency situation, the system becomes unbalanced, and exaggerated processes may occur, involving the same cerebral structures, as well as neurotrophic factors and inflammatory cytokines, producing a form of anxiety that is useless and leads to deleterious effects on the individual, their social environment, relatives, employment, and academic activities – that is, pathological anxiety (Figure 1).

8. Treatments

Anxiety is usually treated with GABA receptor agonists [73]. However, there is a need to develop new treatments that are devoid of the well-known undesirable effects, such as sedation and dependence [74, 75], which can also lead to comorbid depression among other clinical conditions [76].

The aversive stimulation produces anxiety, and a GABAergic activation in basolateral amygdala neurons occurs, but the amygdala also expresses somatostatin, parvalbumin, and cholecystokinin content [77]. Therefore, the control of anxiety involves other processes besides GABAergic action, such as the endocannabinoid receptors located in astrocytes from the accumbens nucleus, which also play a role in the regulation of the stress response [78]. In the extinction of fear, the participation of microglia is relevant; the activated microglia engulf dendritic spines of GABAergic neurons located in the central amygdala in rats exposed to restraint stress [79]. Stress vulnerability is related to the amount of microglia and immunological factors in the

ventral hippocampus [80], and the inactivation of astrocytes in the mPFC enhances anxiety-like behavior and reverses the E/I balance, illustrating a differential role of mPFC astrocytes in the modulation of anxiety [81].

The World Federation of Societies of Biological Psychiatry in 2022 recommended selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and cognitive behavioral therapy as the first-line treatments for multiple forms of anxiety [82]. Additionally, an unexpected new alternative emerged from the success of selective glutamate antagonists, such as ketamine, for the treatment of depression.

The negative allosteric modulation of metabotropic glutamate 7 receptors reduces glutamatergic signaling in the lateral amygdala and diminishes fear and anxiety expression [83]. In rodents, a low dose (10–30 mg/kg) of ketamine produces anxiolytic effects approximately 24 hours later [84]. In a mouse model of posttraumatic stress disorder, a subanesthetic dose of esketamine decreases proinflammatory cytokines and anxiety [85]. Notably, selective serotonin reuptake inhibitor treatment acts on inflammatory cytokines and BDNF in parallel to alleviate anxiety [86]. Other potential treatments that are being successfully tested include antiinflammatory drugs, such as microglia-directed treatments, proinflammatory cytokine inhibitors, cyclooxygenase inhibitors, and other approaches [87]. Similarly, several techniques, including transcranial stimulation, electroconvulsive therapy, deep brain stimulation, and vagal nerve stimulation, appear to exert beneficial effects on anxiety and depression by reducing cytokines and improving microglial activation, thereby mitigating neuroinflammation [88].

Certain current research implies the development of nonsedative benzodiazepines [89] for anxiety treatment. Generalized anxiety is currently successfully treated with duloxetine, escitalopram, pregabalin, quetiapine, and venlafaxine, while other possibilities include ketamine, oxytocin, orexin modulators, endocannabinoids, and, in particular, nonsteroidal agents acting on the immune system [90], antiinflammatory agents [91], and antiinflammatory and immunomodulatory agents [92].

Also, cholecystokinin is considered a good target for anxiety treatment since this substance exerts many actions on the brain, including chronic inflammation, improvement of neuronal synaptic plasticity, prevention of neuronal loss, and modifying the E/I balance by activation of interneurons or inhibition of excitatory neurons in the amygdala [93].

A possible future therapeutic approach may lie in drugs modifying metabolic function, transporters, and receptors of astrocytes [94]. Notably, some approaches for anxiety and depression treatments focus on neuroinflammatory processes through alternatives, including some phytochemical agents [95, 96], neuroactive steroids [97], and cannabidiols [98].

9. Conclusion

Despite extensive basic and experimental research on the pathophysiology of anxiety, there are many unanswered questions. A good approach considers a continuum of actions on neural activity, starting from the natural response to a threatening situation. This response consists of an autonomous reaction that prepares the individual to cope with the threatening situation and successfully

resolve it through a useful adaptive anxiety process. Usually, when the situation is resolved, neural function and levels of cortisol and cytokines return to normal. In several conditions, however, changes in neural function shift to a neuroinflammatory state that involves the abnormal activity of microglia, neurotrophic factors, and inflammatory cytokines. In such cases, a neuroinflammatory process occurs that disrupts corticolimbic circuit function, which is involved in emotion regulation. These findings have been mostly derived from animal studies, including previously stressed animals, and some human studies.

These observations encourage the development of new treatments directed toward mitigating neuroinflammation. The classic explanation for the mechanism of action of anxiolytics involves the GABAergic system, but this is only sufficient for explaining such drugs' sedative actions and is far from providing an adequate explanation for the pathophysiology of anxiety. Considering neuroinflammation as a relevant pathophysiological mechanism that elicits anxiety may eventually support the development of new treatments that target microglia, neurotrophins, and inflammatory cytokines.

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Conflict of Interest

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Recent pronouncements by the World Health Organization consider anxiety as an incapacitating and common pathological entity that affects millions of people worldwide. However, only about one-third of affected individuals receive proper treatment. There is a need to further research into its pathophysiology from a neurobiological perspective and to advance the development of models of this disorder and treatment strategies. Studies should ideally focus on humans, but animal models remain critical. This book presents a collection of studies that have used various animal models and procedures to study and manage anxiety at diverse levels of analysis.

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