What is Stress? Stress Medicine

Abstract

Stress, a pivotal factor in mind-body interactions, remains ambiguously defined, complicating research and clinical practice. This review redefines stress-related terms—stress stimuli, processing, response/sign, feedback loop, and symptom—to clarify their roles in homeostasis, building on Selye's general adaptation syndrome and Cannon's homeostasis framework. We emphasize chronic psychosocial stressors (e.g., social defeat, early-life adversity), which engage limbic circuits and mimic physical stressor symptoms (e.g., fatigue, psychogenic fever), leading to diagnostic confusion. An evolutionary perspective highlights humans' predisposition to stress vulnerability as anxious, social mammals. Stress medicine is an emerging interdisciplinary field that integrates neurobiological, psychological, and clinical approaches to address these complexities. Treatment strategies differentiate biological symptoms, which are managed with pharmacotherapy (e.g., SSRIs for psychogenic fever), from behavioral problems (e.g., rumination, impulsivity), which are addressed through educational interventions like cognitive-behavioral therapy and mindfulness training. A two-step approach, first distinguishing biological and behavioral pathologies, then integrating them, has been shown to optimize care. By elucidating stress mechanisms and treatments, this review lays the foundation for the stress theory series of Core Reports, advancing a holistic understanding of stress-related disorders.

1. Introduction

Stress, a ubiquitous phenomenon, profoundly influences mental and physical health, yet its definition remains elusive due to historical ambiguities and evolving usage. Introduced by Hans Selye in 1936 as a "non-specific response of the body" to external demands, the term "stress" has since been conflated with its causes (stressors) and subjective experiences (distress), leading to confusion in research and clinical practice (Selye, 1936). Originally intended to describe a physiological reaction, "stress" is now widely understood as a state of mental or physical imbalance, particularly in response to psychosocial challenges. This mini-review, part of our inaugural series on stress theory, aims to redefine stress-related terms—stress stimuli, stress

processing, stress response/sign, feedback loop, and symptom—to clarify their roles in maintaining homeostasis. We emphasize the clinical significance of chronic psychosocial stressors, which produce symptoms that mimic physical stressors, complicating diagnosis. An evolutionary perspective highlights humans' predisposition to stress vulnerability, while a new section on stress medicine underscores its emerging role in addressing stress-related disorders.

2. Homeostasis and Stress

The concept of stress is inseparable from homeostasis, defined by Walter Cannon in 1929 as the physiological processes that maintain an organism's steady state amidst external perturbations (Cannon, 1929). The body faces constant challenges, such as temperature fluctuations, pathogens, and psychosocial threats (e.g., social rejection), which threaten internal stability. Homeostasis is maintained through three interdependent components: (1) receptors, which sense internal and external changes; (2) control centers, primarily the brain, which process sensory information; and (3) effectors, which execute responses via peripheral organs or behaviors (Berntson & Cacioppo, 2007).

For example, Cannon observed that cats exposed to a barking dog (a psychosocial stressor) exhibited sympathetic nervous system (SNS) activation, with adrenaline secretion leading to physiological changes such as increased heart rate, dilated pupils, and elevated blood sugar (Cannon, 1929). This "fight-or-flight" response, mediated by the three components, restores homeostasis by preparing the organism for action. However, chronic stressors, particularly psychosocial ones (e.g., repeated social defeat, early-life adversity), can disrupt this balance, leading to chronic physiological dysregulation (McEwen, 1998).

3. Selye's Stress Theory

In 1936, Selye introduced the general adaptation syndrome (GAS), describing a stereotyped, non-specific biological response to intense stimuli, whether physical or mental (Selye, 1936). The GAS comprises three stages: (1) alarm, marked by thymic atrophy and peptic ulcers (6–48 hours); (2) resistance, characterized by adrenal hypertrophy (48 hours–1 month); and (3) exhaustion, leading to death under prolonged stress (1–3 months). Selye identified the hypothalamic-pituitary-adrenocortical (HPA) axis as a key mediator, orchestrating endocrine responses to maintain homeostasis (Selye, 1950).

Selye intended “stress” to denote the body’s response, distinct from its cause (stressor). However, popular usage has blurred these distinctions, with “stress” encompassing both the stimulus and response, often emphasizing psychological distress. Selye later proposed “stressor” for the cause and “stress response” for the reaction, but widespread adoption of “stress” in diverse contexts (e.g., mental strain, physical trauma) has perpetuated confusion (Sapolsky, 2017). This ambiguity complicates research, as some studies refer to “stress” as the response (e.g., cortisol elevation), while others use it for the stimulus (e.g., social isolation).

4. Redefining the Stress-Related Terms

To address this confusion, we propose standardized definitions for stress-related terms, aligning with the three components of homeostasis and incorporating chronic psychosocial stressors.

Stressors (Stress Stimuli)

Stressors, or stress stimuli, are external or internal factors that challenge homeostasis, detected by receptors (the first homeostatic component). These include physical stressors (e.g., cold, injury), chemical stressors (e.g., toxins), biological stressors (e.g., pathogens), and psychosocial stressors (e.g., social defeat, workplace pressure) (Sapolsky, 2017) (Figure.1).

Figure 1. Stress Stimulation (Stressor) and Related Receptor

Stress Category		Stress Types	Stress Stimulation Stress Event	Related Receptor Sensory Organ
Physical stress stimuli (stressors)	Thermal / Mechanical Stress Stimuli (Stressor)	Thermal Stimuli	Heat	TRPV1-4
			Cold	TRPM8
		Mechanical Stimuli		Piezo 1,2
	Chemical Stress Stimuli (Stressor)	Chemical Mediator	H^+	TRPV1/ASIC
			cinnamaldehyde, mustard oil	TRPA1
	Biological (related) Stress Stimuli (Stressor)	Biological thing(s)	Virus, Bacteria, Pollen	
		Inflammatory Cytokine	IL-1β	IL-1β receptor
			IL-6	IL-6 receptor
			TNF-α	TNF-α receptor
		Neurotransmitter	histamine	histamine receptor
			bradykinin	bradykinin receptor
			prostaglandin	prostaglandin receptor
Psychosocial Stress Stimuli (Stressors)		Family relationship-related	loss of loved ones, abuse, poverty	Five senses (eyesight, hearing, taste, smell, touch)
		Work-related	huge works loss of employment	
		Social relationship-related	moving house isolation	

Psychosocial stressors, such as unescapable stress or early-life adversity, are particularly potent in humans due to their reliance on social relationships. These stimuli activate limbic circuits (e.g., amygdala, prefrontal cortex), triggering SNS and HPA axis responses that can mimic physical stressor outcomes, such as fatigue or pain, leading to clinical confusion (Henningsen et al., 2018).

Stress Processing

Stress processing corresponds to the second homeostatic component, the control center (brain), which interprets sensory input from stress stimuli. Information from receptors is relayed to the thalamus and processed by limbic and cortical regions, including the amygdala (emotional valence), hippocampus (memory comparison), and prefrontal cortex (decision-making) (McEwen, 2017). Recent studies highlight distinct processing pathways for psychosocial versus physical stressors. For example, psychosocial stressors enhance amygdala-prefrontal connectivity, amplifying emotional reactivity, whereas physical stressors primarily engage brainstem pathways

(Shackman & Fox, 2021). These differences influence clinical presentations and treatment efficacy, necessitating precise terminology in research.

Stress Response and Sign

The stress response, mediated by effectors (the third homeostatic component), encompasses the body's physiological and behavioral reactions to processed stimuli. Selye defined stress as "the nonspecific response of the body to any demand," referring to this response (Selye, 1936). Responses include SNS activation (e.g., increased heart rate), HPA axis activation (e.g., cortisol release), and behavioral adaptations (e.g., avoidance). These responses produce measurable signs, such as vital signs (body temperature, blood pressure) or biomarkers (cortisol levels, inflammatory cytokines) (Russell & Lightman, 2019).

Chronic psychosocial stressors, such as repeated social defeat or early-life stress, induce prolonged HPA axis and SNS overactivation, leading to allostatic overload. This manifests as signs like psychogenic fever, fatigue, or pain, which overlap with physical stressor symptoms, confusing clinicians (Henningsen et al., 2018). For example, chronic social isolation can elevate cortisol and inflammatory markers, mimicking infectious disease symptoms, yet standard tests (e.g., CRP, imaging) may be normal.

Feedback Loop

Feedback loops are critical for maintaining homeostasis, as signs from stress responses are detected by receptors and relayed back to the brain for adjustment. For instance, elevated cortisol inhibits HPA axis activity via negative feedback, restoring balance (Russell & Lightman, 2019). Chronic stress disrupts these loops, leading to glucocorticoid receptor resistance and sustained hypercortisolemia (Zannas et al., 2019). Individual differences, such as heightened mucosal sensitivity under psychosocial stress, modulate feedback efficacy, influencing symptom perception (Foster et al., 2017).

5. Stress Medicine

Stress Medicine is an interdisciplinary field dedicated to a holistic understanding and management of stress-related disorders. Stress medicine focuses on three core principles for effective patient care: 1) identification of the primary stressor(s), 2) analysis of the individual's stress processing mechanisms, and 3) characterization of abnormal physiological and psychological stress responses (signs and symptoms). Even a single sign, such as a fever, can be accompanied by a variety of stress stimuli (stressors), and symptoms will not improve unless appropriate treatment is selected.

Stress medicine recognizes that chronic psychosocial stressors produce symptoms (e.g., fatigue, pain, anxiety) that overlap with physical disorders, necessitating holistic approaches to diagnosis and treatment. Furthermore, stress medicine recognizes the difference between symptoms caused by biological problems and symptoms caused by behavioral problems. Symptoms caused by biological problems are treated using a medical model that takes an approach to reduce or eliminate the stressor (stress stimulus), while symptoms caused by behavioral problems are treated using an educational model that encourages behavioral growth to reduce the abnormal harmful behaviors that cause the symptoms.

Stress medicine, though not fully integrated into mainstream medical practice, is an emerging interdisciplinary field that addresses stress-related disorders through neurobiological, psychological, and clinical lenses. It encompasses the study of stress mechanisms (e.g., HPA axis dysregulation, neuroinflammation) and interventions aimed at mitigating their impact (Cohen et al., 2019). By including these insights into research and treatment, stress medicine aims to bridge mind-body interactions, guiding future research and therapeutic strategies.

Symptoms

Symptoms arise when the host perceives a sign as abnormal, often accompanied by distress. Unlike signs (objective, measurable), symptoms are subjective and mediated by cognition. For example, a body temperature of 38°C may be a sign, but only becomes a symptom (fever) if recognized as distressing. Conversely, normal signs (e.g., 36°C) may be perceived as

symptoms if receptors are hypersensitive, as seen in functional somatic syndromes (Henningsen et al., 2018). Psychosocial stressors exacerbate this discrepancy, producing symptoms like fatigue or pain that lack clear biomarkers, complicating diagnosis.

Biological Symptoms

Biological symptoms are the physiological changes that occur within an organism due to the acute or chronic impact of stressors (Figure 1). While traditionally, physical stressors are readily acknowledged for eliciting robust biological reactions, it is crucial to recognize that psychosocial stressors are equally potent activators of these fundamental biological stress responses. Physical stressors, such as infections or injuries, primarily activate brainstem-mediated pathways, engaging the HPA axis and inflammatory cascades to produce symptoms like fever, pain, or fatigue (Herman et al., 2016). For example, fever from bacterial infection is driven by cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2), responding to antipyretics like ibuprofen (Oka, 2018). Physical stressors also induce psychiatric symptoms; for instance, viral infections can trigger depressive states via neuroinflammatory cytokines (e.g., IL-6), which disrupt monoamine metabolism (Dantzer et al., 2008).

Psychosocial stressors, such as loss of loved ones, unemployment, or chronic workplace stress, engage limbic circuits (e.g., amygdala, ventromedial prefrontal cortex [vmPFC], dorsomedial hypothalamus [DMH]), leading to SNS and HPA axis hyperactivity (McEwen, 2017). These stressors produce both psychiatric symptoms (e.g., depression, anxiety) and somatic symptoms (e.g., psychogenic fever, appetite loss, palpitations), which can mimic physical disorders (Henningsen et al., 2018). For instance, psychogenic fever, mediated by the vmPFC→DMH pathway, is refractory to antipyretics but responds to anxiolytics (e.g., benzodiazepines) or selective serotonin reuptake inhibitors (SSRIs) by modulating serotonergic and limbic activity (Nakamura et al., 2020). Similarly, appetite loss from psychosocial stress, linked to vagal suppression and hypothalamic dysregulation, may improve with SSRIs or psychotherapy (Konturek et al., 2011).

Somatic symptoms induced by psychosocial stressors, such as chronic fatigue or diffuse pain, often lack objective biomarkers, leading to their frequent classification as “medically unexplained symptoms” (MUS) in internal medicine (Henningsen et al., 2018). Historically, these symptoms

have been undertreated, as standard diagnostic tests (e.g., MRI, blood panels) fail to detect functional impairments in limbic or autonomic networks. In contrast, psychiatric symptoms from psychosocial stressors, such as depression or anxiety, are typically managed by psychiatrists using evidence-based treatments like cognitive-behavioral therapy (CBT) or pharmacotherapy (Cohen et al., 2019).

Behavioral symptoms

Behavioral symptoms are maladaptive (immature) behaviors. In contrast to biological symptoms, behavioral symptoms refer to observable patterns of action, thought, or emotional expression that are initiated, altered, or exacerbated by stress. These are distinct from direct biological signs but are deeply rooted in stress-induced neurobiological dysregulation. Chronic stress, whether from physical (e.g., chronic illness) or psychosocial (e.g., social defeat, early-life adversity) stressors, can also precipitate behavioral symptoms, such as ruminative thinking, impulsivity, compulsive behaviors, or aggression, which are distinct from biological symptoms but share neurobiological roots (Arnsten, 2015). These symptoms arise from stress-induced dysregulation of prefrontal cortex (PFC) and amygdala connectivity, impairing executive functions like impulse control, decision-making, and emotional regulation (McEwen, 2017). For example, chronic psychosocial stress enhances amygdala-driven emotional reactivity while weakening PFC-mediated inhibition, leading to ruminative thinking in depression or impulsivity in anxiety disorders (Shackman & Fox, 2021).

While biological symptoms (e.g., psychogenic fever, palpitations) are often treated within a medical model using pharmacotherapy (e.g., SSRIs, anxiolytics) or targeted interventions (e.g., antipyretics), behavioral problems require an educational model focused on fostering adaptive behaviors and neuroplasticity (Hofmann et al., 2012). Developmental factors, such as limited real-world experiences or inadequate social learning during critical periods, exacerbate stress-related behavioral issues, particularly in adolescents or young adults. For instance, ruminative thinking, a hallmark of depression, stems from overactive default mode network (DMN) activity under chronic stress, perpetuating maladaptive cognitive patterns (Hamilton et al., 2015). Similarly,

compulsive eating in response to stress reflects learned maladaptive coping, not solely biological dysfunction.

Integrated Treatment Approach

Effective treatment of stress-related disorders requires a two-step approach within the stress medicine framework: (1) distinguishing biological symptoms from behavioral problems, and (2) integrating both for personalized care (Figure 2).

Figure 2. Treatment (Medicine) for symptom in each category

		Symptoms (expression)	
		Physical (somatic) Symptom	**Psychiatric (mental, psychological) Symptom**
Trigger	**Physical Stress Stimuli (Stressor)**	Internal medicine, Surgery, Pediatrics	Liaison support (ex: anxiety in cancer patient)
	Psychosocial Stress Stimuli (Stressor)	Psychosomatic Medicine	Psychiatric Medicine

Initially, clinicians must differentiate biological abnormalities (e.g., elevated cortisol, psychogenic fever) driven by stress stimuli and responses from behavioral issues (e.g., rumination, impulsivity) influenced by stress-exacerbated developmental or learned deficits. For instance, a patient with chronic workplace stress may present with palpitations (biological, treatable with beta-blockers or SSRIs) and ruminative thinking (behavioral, treatable with CBT). Diagnostic tools, such as stress questionnaires (e.g., Brain Overwork Scale, to be discussed in later reviews) or functional neuroimaging, can aid in this differentiation (Hamilton et al., 2015).

Subsequently, treatment plans must integrate biological and behavioral interventions to address the multifaceted impact of chronic stress. Multidisciplinary teams, including psychiatrists, psychologists, and educators, can tailor strategies, combining pharmacotherapy (e.g., SSRIs for depression), psychotherapy (e.g., CBT for rumination), lifestyle interventions (e.g., exercise for

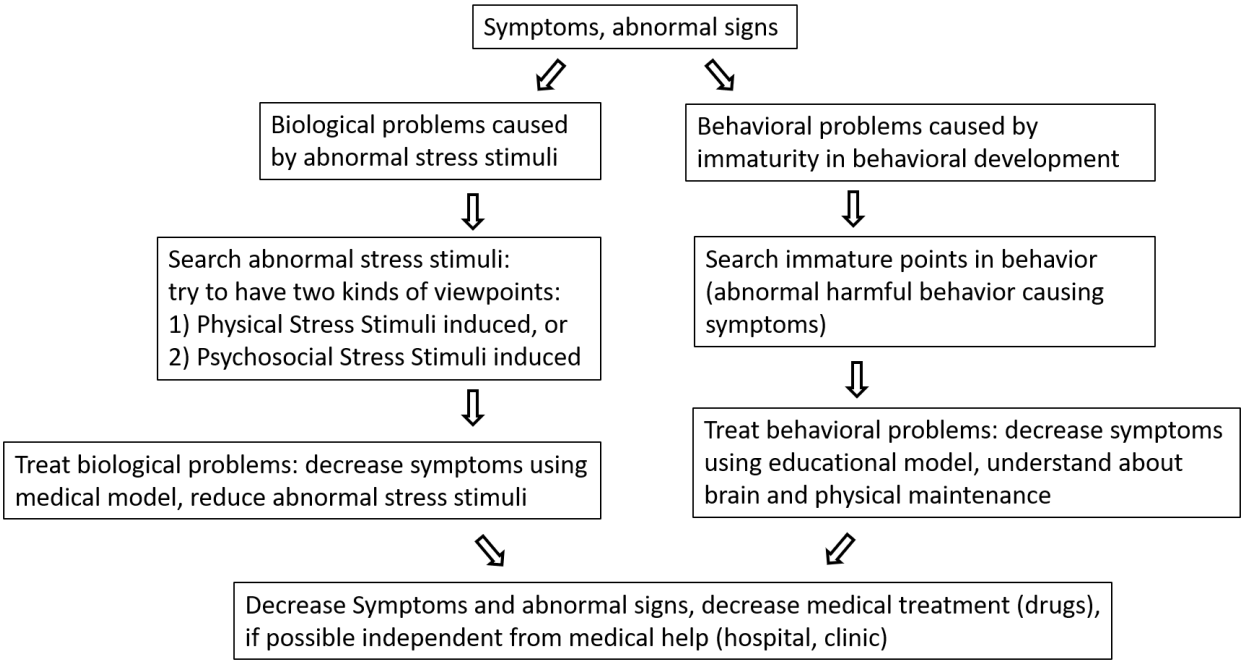
allostatic load reduction), and behavioral training (e.g., social skills for impulsivity) (Cohen et al., 2019). This integrative approach recognizes that chronic stress often involves intertwined physical and psychosocial stressors, necessitating comprehensive care. For example, a patient grieving a loss may require SSRIs for appetite loss, CBT for rumination, and social support to rebuild adaptive behaviors.

In clinical practice, patients often present symptoms arising from intertwined physical and psychosocial stressors, necessitating a multidisciplinary approach within the stress medicine framework. For example, a patient with a viral infection may experience fever (physical stressor) and depression (psychosocial amplification), requiring antipyretics and psychological support. Conversely, a patient grieving a loss may exhibit depression and appetite loss (psychosocial stressor), benefiting from SSRIs and nutritional counseling. Treatment strategies should include:

- Pharmacotherapy: SSRIs (e.g., sertraline) or anxiolytics for psychosocial stress-induced symptoms; antipyretics or antibiotics for physical stressors (Oka, 2018).
- Psychotherapy: CBT or mindfulness-based stress reduction to mitigate HPA axis hyperactivity and enhance coping (Cohen et al., 2019).
- Lifestyle Interventions: Exercise, sleep hygiene, and social support to reduce allostatic load (McEwen, 2017).
- Diagnostic Tools: Stress questionnaires (e.g., Brain Overwork Scale, to be discussed in later reviews) and autonomic monitoring to identify stressor types.

Stress medicine advocates for research that links stressor-specific mechanisms to treatment outcomes, unraveling the complex interplay of physical and psychosocial factors. By identifying which stressors predominate and how they affect neural and physiological systems, clinicians can tailor interventions, improving outcomes for stress-related disorders (Figure 3).

Figure 3. Strategy in treating symptoms (patients)



6. Evolutionary Perspective

Humans' stress responses are shaped by their evolutionary history as small, anxious mammals in predator-rich environments. As a species, humans evolved heightened anxiety to detect threats, with genetic predispositions (e.g., serotonin transporter gene polymorphisms) enhancing stress sensitivity (Nesse, 2019). Unlike acute threats faced by ancestral mammals, modern psychosocial stressors (e.g., social exclusion, workplace demands) are often chronic and unescapable, overtaxing evolved stress systems. Humans' dependence on social relationships, a survival trait, amplifies vulnerability to psychosocial stressors, as disrupted social bonds trigger stress responses akin to physical threats (Sapolsky, 2017). This evolutionary mismatch underscores the clinical significance of chronic stress and its diagnostic challenges.

7. Conclusion

Chronic psychosocial stressors, rooted in humans' evolutionary predisposition to anxiety and social dependence, produce symptoms that mimic physical stressors, confounding clinicians, nowadays. Stress, a dynamic interplay of stimuli, processing, and responses, is central to mind-body interactions. By redefining stress-related terms-stress stimuli, processing, response/sign, feedback loop, and symptom we clarify Selye's original intent while addressing modern complexities. This redefinition sets the stage for stress theory series of *Core Reports*, offers a framework to integrate various insights, including Stress Medicine and Coro Heart Medicine, paving the way for precise research and treatment, and advance our understanding of the mind's role in health and disease.

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