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The Impact of Psychological and Social Stress on General and Public Health.

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In Loving Memory of Late Professor Doctor ""Mohamed Refaat Hussein Mahran""

Abstract

Aim: This study aims to explore the extensive impact of psychological stress on health, focusing on cognitive functions, cardiovascular health, and immune responses. By synthesizing findings from recent research, we aim to elucidate the mechanisms through which chronic stress affects these domains and propose potential pathways for intervention. **Methods:** A comprehensive review of the literature was conducted, examining studies on stress and its impact on prospective memory (PM), autonomic nervous system, mitochondria, hormones, cardiovascular parameters (blood pressure reactivity and heart rate variability), and immune function. Key studies involving neuroimaging, physiological monitoring, and biochemical analyses were included to provide a holistic understanding of the stress-health relationship. **Results:** Chronic psychological stress impairs high-order cognitive functions, particularly PM, through hippocampal dysfunction mediated by glucocorticoid dysregulation. Cardiovascular health is compromised by stress-induced autonomic imbalance, leading to elevated blood pressure and reduced heart rate variability. This imbalance contributes to increased allostatic load and a higher risk of cardiovascular diseases. Additionally, stress modulates immune responses by activating the HPA axis, resulting in altered inflammation levels and immune dysfunction. **Conclusion:** The findings highlight the pervasive impact of psychological stress on multiple health domains. Chronic stress leads to significant cognitive impairments, cardiovascular dysfunction, and immune dysregulation. Understanding these mechanisms is crucial for developing targeted interventions to mitigate the adverse effects of stress on health. Future research should focus on personalized approaches to stress management, considering individual differences in stress responses and resilience.

Key Words: Psychological stress, prospective memory, hippocampus, cardiovascular health, autonomic nervous system, blood pressure, heart rate, allostatic load, glucocorticoids.

Introduction:

Stress is now a necessary component of everyday language and the human experience. Since troops in World War I displayed shellshock, an extreme response to combat trauma that would later be identified as post-traumatic stress disorder, scientists have been interested in stress [1]. Growing public awareness of stress and its consequences and a notable increase in research have coincided over the years with greater media coverage of stress. Stress is recognized as a major contributor to long-term sickness worldwide, accounting for millions of missed workdays [2-3]. Stress appears on Time magazine covers, in best-selling books, and as a major theme in plays, movies, and novels. The fact that stress affects everyone and permeates every part of life is what piques our interest in it. It is also widely known that stress can impact health both directly—via changes in autonomic and neuroendocrine responses, which are the subject of this review—and indirectly—through changes in health-related behaviors [4-6]. Stress may indirectly

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raise the risk of obesity, heart disease, and cancer by altering diets negatively and promoting bad eating habits such consuming a lot of fat or little fiber and fruits and vegetables.

However, there has been a recent examination of the concept of stress. According to Kagan (2016), the mere fact that an event causes a change in behavior or biology qualifies it as a stressor, which reduces its usefulness [7]. He proposed that situations that seriously jeopardize an organism's survival should only be referred to as stressful events. Renowned academics and theorists have contested this viewpoint. According to one group, the idea of stress is still useful when viewed scientifically in the larger framework of allostasis and allostatic load, which includes adjusting to both good and bad life experiences and the health-related behaviors that follow [8]. In a persuasive argument, another group has maintained that stress functions as a helpful heuristic that allows different traditions in stress research—biological, psychological, and epidemiological—to be integrated into a stage model of stress and disease [9]. Segerstrom and O'Connor (2012) pointed out that although the idea of stress has a positive history, some people disagree with it and believe it should be applied more precisely and simplistically. One might identify stress in the following ways: in response to a stressor, such as an emotional or physiological reaction, in assessment, such as the degree to which a hazardous encounter is viewed as stressful, or in the environment, such as a noxious stimulus. To distinguish between these locations and comprehend how they interact, thorough conceptualization and assessment are therefore required. Slavich (2019) expressed similar concerns when he coined the word "stressnology" to draw attention to the inadequate and flawed methods of examining how stress affects human health. He recommended better assessment techniques and the use of cutting-edge tools. Notwithstanding these obstacles, the body of research demonstrating the detrimental effects of stress on health outcomes is strong. The importance of stress in health is highlighted by the durability of these associations, despite doubts about the accuracy of stress measurement and conceptualization [10].

Two main physiological systems are triggered when someone experiences extreme stress. Heart rate (HR) and blood pressure (BP) are raised as a result of the neurological system's instant activation of the sympatho-adrenal medullary (SAM) system, which releases catecholamines, adrenaline, and noradrenaline [11]. Increased salivary alpha-amylase levels are another sign of this activation [12-13]. Simultaneously, the hypothalamo-pituitary-adrenal (HPA) axis is activated by the endocrine system in response to acute stress, causing the adrenal cortex to secrete cortisol [11]. Both systems must be activated in order for the body to be ready to face the perceived threat and to return to equilibrium after it has passed. Responses to acute psychological stressors, or active-coping stressors, are deemed “metabolically unjustified” in contrast to physical stressors because body fuel reserves are used for an involuntary activity [14]. Pathological disorders may be exacerbated by these physiologically illogical responses [14]. Researchers and medical professionals have been examining the possibility of a relationship between acute psychological stress response and health and illness outcomes for many years. In order to gain a better understanding of stress responses, a considerable amount of time and resources have been devoted by researchers worldwide to assessing psychological stress reactivity. The number of articles in this topic has increased significantly over the last 20 years, as evidenced by a Web of Science search for "psychological stress reactivity": 131 in 1998, 258 in 2008, and 430 in 2018. An understanding of the association between acute psychological stress reactivity and future outcomes related to physical and mental health as well as disease is critical in order to contextualize the findings from such investigations, particularly those from cross-sectional studies that do not show causation [15]. In spite of a great deal of research, the role that psychological stress reactivity plays in long-term outcomes related to physical and mental health as well as disease [16-20].

According to theories that date back to 1981, there may be a greater risk of developing hypertension if there are increased cardiovascular reactions to acute psychological stresses (also known as active-coping stressors) [21]. Numerous reviews [22-24] and meta-analyses [25-26] have supported the "reactivity hypothesis," which has been the subject of extensive research. Many problems remain unresolved, nevertheless, as the original reactivity hypothesis was restricted to the relationship between the consequences of cardiovascular illness and excessive cardiovascular reactivity. Is it crucial for health, for example, for non-cardiovascular measurements like cortisol, salivary alpha-amylase, and catecholamines to react in parallel? Is there a correlation between muted reactivity and the outcomes of diseases and future physical and mental health? Is there a connection between earlier psychological stress reactivity and outcomes related to health and diseases other than cardiovascular disease?

Recent studies have investigated the impact of muted reactivity in future health and illness outcomes, including those outside cardiovascular disease, while earlier research focused on excessive reactivity [18]. Disparate discoveries are dispersed across many disciplines and illness states as the body of information in this topic expands; these findings frequently go unreported in other pertinent fields.

Cardiovascular reactivity has been the only subject of earlier systematic syntheses [25-26] or particular data sets [18]. There are still a lot of unsolved concerns in this area, so a thorough systematic review of the research is necessary. In conclusion, stress is a multifaceted concept deeply embedded in the human experience and significantly impacting health. Despite debates over its precise definition and measurement, the cumulative evidence underscores the importance of understanding stress reactivity. Acute stress responses, involving both the sympatho-adrenal medullary and hypothalamo-pituitary-adrenal systems, play crucial roles in health outcomes. Future research should aim for a broader systematic review to integrate findings across disciplines and provide a more comprehensive understanding of how stress reactivity influences both physical and mental health. This approach will help clarify unresolved questions and improve our ability to address the negative health impacts of stress.

Stress and Health: Basic Concepts

The basic concept of homeostasis is how the human body adjusts to shifting internal and external surroundings in order to survive. To maintain life, this entails closely controlling internal physiological states including body temperature and oxygen levels. The body adjusts to everyday activities, including stressful ones, by activating the autonomic nervous system (ANS) and central nervous system and releasing chemicals like cortisol, adrenaline, and noradrenaline. Allostasis [27] refers to the release of various physiological mediators and modifications in immunological and metabolic parameters that are protective and adaptive as long as they are properly regulated and end when the environmental challenge or stressor passes. On the other hand, frequent or extended activation of these reactions may be harmful to one's health.

The term "allostatic load" was first used by McEwen (1998) to describe the cumulative damage that chronic stress exposure causes to the body. He pointed out that ineffective control of stress mediators, which can cause an overreaction or an inadequate response to stress, is the root cause of allostatic load. An imbalance in physiological reactions, such as the improper release of cortisol during acute stress, may result from this. In addition, McEwen proposed that chronic stress affects metabolic, neurological, cellular, cardiovascular, and behavioral processes, raising the risk of disease by reducing the efficiency of body systems [28]. More recently, allostatic overload—the negative consequences of long-term stress on biological systems—was covered by McEwen (2018), who built on this. This happens when stress mediators are engaged excessively, repeatedly, and chronically, which eventually leads to harm. The influence of stress on various biological systems and the way in which these systems interact to regulate and react to perceived environmental stressors are highlighted by allostatic overload.

Stress Responses:

There are two main systems that get triggered when we are under stress. The hypothalamic-pituitary-adrenal (HPA) axis is triggered second, after the sympathetic–adrenal–medullary (SAM) system, which is the first and most quickly activated. The brain—more especially, the amygdala and subsequently the hypothalamus—fast activates the autonomic nervous system (ANS) in response to an abrupt danger or fear. This signal causes the adrenal glands to release noradrenaline, which stimulates internal organs. This is the standard sympathetic reaction of the ANS to a danger. In order to further prime the body for action, the adrenal medulla simultaneously produces adrenaline, which is quickly absorbed by the circulation. This is the response of the SAM system. Adrenaline and noradrenaline cause the body to become hypervigilant in a matter of seconds, triggering the fight-or-flight reaction. This causes dilated pupils to let in more light, quick breathing, an increase in heart rate and strength, and a decrease in digestive activity to direct blood supply to the muscles. This reaction happens quickly and strongly.

When a person experiences a stressful environmental event, the hypothalamus also releases a peptide hormone known as corticotrophin-releasing factor (CRF), in addition to the SAM reaction. Adrenocorticotrophic hormone (ACTH) is released by the pituitary gland in response to CRF, which enters the bloodstream and travels there. The glucocorticoid cortisol, sometimes known as the stress hormone, is produced when ACTH travels to the adrenal cortex. Increasing access to energy stores, improving the mobilization of protein and fat, and lowering inflammation are among cortisol's main actions. When under stress, the body releases glycogen—a stored form of energy—from the muscles and liver. The glycogen is then transformed into glucose, which the body and brain can use. Cortisol, however, is a complicated hormone that functions in a variety of ways outside of the stress response [29]. For example, cortisol influences both genetic and non-genomic cellular and molecular pathways, which are important for the regulation of circadian rhythms.

This review will go into additional detail about the consequences of repetitive and chronic stress exposure on physical and mental health outcomes, which have been studied by many researchers since Selye's groundbreaking discoveries. Simultaneously, there has been a great deal of interest in clarifying the basic biological processes that mediate the connection between stress and health. This entails looking into the exact mechanisms by which stress raises the likelihood of

developing a disease, speeds up the course of an illness, and shortens life expectancy. Important inquiries come to mind, like: Which biological systems are disturbed by stress prior to its manifestation in health outcomes? How can stress affect the expression of genes that could affect health? There has been a lot of study, therefore this review won't try to cover everything. Rather, it will focus on three key research areas that have greatly advanced our knowledge of the relationship between stress and health: (a) how stress affects cortisol dynamics and the regulation of the hypothalamic-pituitary-adrenal (HPA) axis; (b) how stress affects the autonomic nervous system (ANS), specifically blood pressure (BP) and heart rate variability (HRV); and (c) recent developments in social genomics that show how environmental factors, including stress, can affect gene expression.

Effect of Stress on Hormones:

The main hormone in charge of the HPA axis stress response mechanism is cortisol. The hypothalamus and pituitary glands cortisol receptors monitor cortisol levels, which drives the HPA axis through a negative feedback mechanism. Low amounts of cortisol drive additional secretion, while high levels prevent it. But persistent HPA axis activation raises cortisol levels, which exposes body tissues to too much hormone [30-31]. This chronic activation puts undue strain on many bodily systems, including the HPA axis (i.e., allostatic load and overload), which can result in tissue damage and lead to further health problems.

Many studies have examined whether those who have heightened cortisol responses to stress are more likely to experience health issues in the future [32-35]. These studies highlight that people who have the greatest rises in blood pressure or heart rate in reaction to acute stress are most likely to experience health problems in the future. This idea is influenced by the reactivity hypothesis, which was first applied to cardiovascular reactivity [14]. Higher cortisol reactivity to stress has been associated with negative health outcomes, according to a number of significant studies [36-39]. For instance, Hamer et al. (2010) connected increased stress reactivity to coronary artery calcification, whereas al'Absi & Wittmers (2003) discovered that increased HPA activity in response to acute stress was associated with hypertension risk. Hamer & Steptoe (2012) found that for every standard deviation shift in cortisol response, there was a 59% increase in incident hypertension in the Whitehall II cohort research. Three years later, this cohort similarly showed a correlation between increased cortisol reactivity and the advancement of coronary artery calcification [39]. A connection between cortisol responsiveness, stress, and cellular aging has been suggested by Steptoe et al. (2017)'s discovery that cortisol responders to acute stress had shorter telomeres three years later.

Additionally, studies have shown that reduced or dull cortisol responses to stress may be an indication of present illness or potential danger to health in the future [30]. According to early research on patients with alcohol dependence, addicts did not significantly increase their cortisol levels after stress tests; this suggests that decreased responses could be a marker of dysregulation of the HPA axis [40]. Recent research, while less so in the last 20 years, has demonstrated a connection between chronic stress and poor health outcomes and reduced cortisol responsiveness to stress [41, 35]. For example, Padden et al. (2019) discovered that the main characteristic of caregivers of people with autism spectrum disorder was decreased cortisol response [42]. In a similar vein, people who had tried suicide had lower cortisol levels than controls, according to O'Connor et al. (2017). A strong correlation was discovered in a meta-analysis of early-life adversity between early adversity and reduced cortisol reactions to social stress [32]. Overall, the data point to a connection between elevated risks for future health and both muted and heightened cortisol reactions to acute stressors. Carroll et al. (2017) put out a model that combined heightened and attenuated stress reactions, implying a nonlinear inverted-U connection in which elevated as well as decreased cortisol levels are harmful. For other hormones and significant actions, this association is comparable.

The diurnal cortisol slope, which represents the gradual drop in cortisol levels throughout the day, and the cortisol awakening response (CAR), which peaks soon after waking, are the two distinct components of the cortisol production pattern that occurs throughout the day [43-46]. Since cortisol is essential for the regulation of many biological systems, such as the immunological, inflammatory, and metabolic processes, irregularities in its circadian rhythm can have long-term negative effects on these systems as well as general health [47-48]. We'll take a quick look at the many studies that have looked into the relationship between diurnal cortisol levels and health consequences. But first, the connection between stress and the CAR is considered.

Recent studies have focused on the cortisol response (CAR), which is the sharp rise in cortisol that occurs in the first 30 to 45 minutes after waking; however, its exact mechanism and control are still unknown. Research indicates that the cortisol released during the rest of the day is not regulated in the same way as the CAR. Theoretically, the CAR gets people ready for the demands of the day [49]. A variety of studies [50-54] have found mixed links between the CAR and stress and different health outcomes. According to some studies [55-56], stress raises the CAR. However, other research [57-58]

demonstrates that chronic stress can disrupt HPA axis regulation, blunting the CAR. A thorough meta-analysis conducted by Chida & Steptoe (2009) revealed that a number of psychosocial factors are connected to both increased and decreased CAR in terms of health outcomes. In particular, there was a negative correlation found between the CAR and weariness, burnout, exhaustion, and post-traumatic stress disorder, but a positive correlation with job stress and overall life stress. Boggero et al. (2017) discovered inconsistent results as well, linking post-traumatic stress disorder to lower CAR and depression to higher CAR [59]. These inconsistent results were probably caused by methodological problems, such as protocol infractions. Since protocol adherence affects the accuracy of the CAR measurement, future study should limit nonadherence to lower data variability [60].

According to Steptoe & Serwinski (2016), circumstances demanding active coping with daily demands may show a higher CAR, whereas extreme stress that prevents active coping may show a lower CAR. Alternatively, allostatic stress and overload may account for inconsistent results. While lower CAR in the context of burnout, PTSD, and fatigue may indicate HPA axis dysregulation as a result of chronic severe stress (allostatic overload or toxic stress), moderate to high CAR during times of increased demand may reflect an adaptive response to a stressful environment (allostatic load) [61]. This perspective is consistent with meta-analytical data that links chronic stress to malfunction of the HPA axis [62] and cortisol responses to suicide risk. All things considered, the CAR is a noteworthy measure of HPA axis activity and offers insightful information on the interactions among psychological variables, HPA axis function, health, and well-being. Like cortisol reactivity to stress, there may be health hazards linked to both high and low CAR. Future studies should use longitudinal designs and frequent evaluations to clarify the specific regulatory role of the CAR.

Effect of Stress on CNS:

The hypothesis that chronic exposure to high levels of glucocorticoids (GCs) may have neurotoxic effects on the brain originated from studies on aging animals. In both animals and humans, aging is marked by variability in physiological functioning and cognitive performance, influenced in part by hypothalamic-pituitary-adrenal (HPA) axis activity. Early 1990s studies in rats indicated that elevated basal GC levels in aged rodents, observed in about 30% of the population, are not typical of normal aging but rather associated with memory impairments [63-64]. These impairments were linked to increased HPA-axis activity. The hippocampus, crucial for learning and memory, was identified as particularly vulnerable to GCs due to its high concentration of GC receptors [66-67].

Research in animals demonstrated that chronic exposure to high GC levels is linked to cognitive deficits, especially in tasks dependent on the hippocampus like spatial memory [68-69]. Behavioral findings were paralleled by structural changes in the hippocampus, including neuronal loss, dendritic atrophy, reduced volume, and decreased neurogenesis [70-72]. Despite age being a risk factor, studies revealed that it's not a direct predictor of cognitive decline under GC exposure. Middle-aged rats exposed to prolonged high GC levels showed memory deficits similar to those seen in aged rats with naturally elevated GC levels. Conversely, reducing GC secretion appeared protective against spatial memory impairments in aging, linked with increased neurogenesis [73]. These findings gave rise to the Glucocorticoid Cascade Hypothesis [74], now known as the Neurotoxicity Hypothesis. This theory suggests that prolonged exposure to elevated GC levels can disrupt HPA-axis regulation, leading to cumulative detrimental effects on hippocampal structure and memory function.

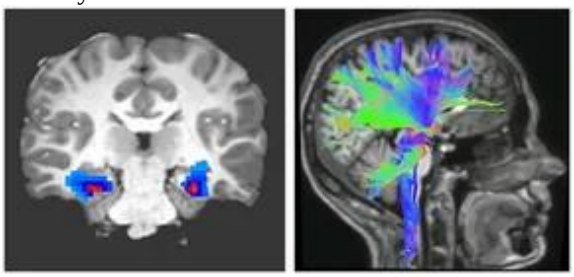

Figure 1: Effect of Stress on Brain cells. Functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) are widely used techniques to assess brain connectivity. fMRI measures neural activity between regions by analyzing changes in the blood oxygen level-dependent (BOLD) MRI signal. DTI, in contrast, measures structural connectivity by mapping white matter tracts. Fractional anisotropy (FA), derived from DTI, indicates the degree of directional water diffusion, with higher FA values suggesting greater myelination or organization of white matter tracts.

Effect of Stress on Blood Pressure and Heart Rates:

The literature on the effects of psychological stress on blood pressure (BP) responses and autonomic nervous system (ANS) dynamics highlights significant associations with long-term health outcomes.

1. **Blood Pressure Response to Psychological Stress:**
   - Gasperin et al. (2009) conducted a meta-analysis of cohort studies involving over 34,000 participants, finding that greater BP responses to psychological stress were associated with a 21% increased risk of elevated BP 11 years later. This suggests that

managing psychological stress could be crucial in hypertension management [75].

- Landesbergis et al. (2013) reported that job strain is linked with higher ambulatory systolic and diastolic BP during working hours, at home, and even during sleep. The lack of BP dipping at night, a period that should represent safety, is associated with adverse cardiovascular outcomes such as left ventricular hypertrophy, myocardial infarction, and stroke [76].

2. **Autonomic Nervous System (ANS) Imbalance and Health Outcomes:**

- High heart rate (HR) and low vagally mediated heart rate variability (HRV) are indicative of ANS imbalance and have been consistently linked to poor health outcomes.
- Jarczok et al. (2013, 2020) reviewed studies showing that adverse work conditions generally lead to decreased HRV, emphasizing its association with increased risk for cardiometabolic and inflammatory diseases [77-78].
- Kivimäki & Steptoe (2018) reviewed large studies showing hazard ratios ranging from 1.13 to 2.07 for the association between psychological stressors (like work stress and childhood stress) and cardiovascular disease, coronary heart disease, and stroke. However, evidence for effective interventions to mitigate these risks remains scarce [79].

3. **Circadian Variation in ANS Activity and Stress:**

- Nighttime is supposed to be a period of relative safety with decreased sympathetic nervous system (SNS) and increased parasympathetic nervous system (PNS) activity. Elevated HR and BP at night are associated with increased mortality.
- Both acute and chronic stress have been linked to blunted increases in HRV at night, which is crucial for cardiovascular health.
- Psychological factors such as stress, job strain, hostility, perceived discrimination, social integration, and social support have been shown to influence nighttime BP dipping, where salubrious factors are associated with greater BP dipping and deleterious factors with less dipping.

4. **Integration and Future Directions:**

- Models like the Generalized Unsaturated Theory of Stress (GUTS) aim to integrate these complex relationships, suggesting that both exaggerated and blunted responses to stress may contribute to poor health outcomes over time.
- Future research should focus on elucidating the mechanisms linking psychological stress, ANS function, and circadian variations in health outcomes to develop more effective interventions.

In summary, the impact of psychological stress on BP responses and ANS dynamics underscores its critical role in cardiovascular health. Effective management of stress could potentially mitigate these adverse effects, highlighting the importance of integrating psychological and physiological approaches in clinical and public health interventions.

Effect of Stress on Mitochondria:

The concept of allostatic load (AL) and allostatic overload (AO) elucidates how the body adapts to stress through various physiological systems such as cortisol, the autonomic nervous system, metabolic processes, and immune responses to maintain homeostasis. AL refers to the cumulative impact of multiple stressors and dysregulation in these systems, which can manifest as excessive or inadequate levels of cortisol, adrenaline, prolonged inflammation, and other physiological responses. AO, on the other hand, describes the pathophysiological changes that occur when these adaptive systems become dysregulated over time, affecting cellular and organ functions. Mitochondria, often referred to as the powerhouses of cells, play a crucial role in both AL and AO. They respond to stress mediators by undergoing structural and functional adaptations, such as changes in hormonal receptor activation, mitochondrial dynamics (fusion/fission), and production of reactive oxygen species (ROS). Prolonged exposure to stressors can lead to mitochondrial damage, including mutations in mitochondrial DNA (mtDNA), alterations in mitochondrial content, and reduced energy production capacity. These mitochondrial changes contribute to signaling pathways involving traditional AL biomarkers (e.g., lipids, glucose) and other processes like gene dysregulation, oxidative stress, inflammation, and cellular senescence [80].

The term Mitochondrial AL (MAL) encompasses the multifaceted alterations in mitochondrial biology induced by chronic stressors. This includes quantitative changes in mitochondrial parameters (e.g., ATP synthesis, ROS production) and qualitative changes in physiological functions (e.g., mitochondrial dynamics, substrate preference). Unlike traditional AL biomarkers, which are static entities like proteins or metabolites, mitochondria are dynamic living entities. Therefore, MAL is best quantified through measures that reflect these dynamic functions, such as enzymatic activities over time, rather than static protein concentrations. Developing robust MAL measures is crucial for understanding the effects of psychosocial stress on mitochondrial function and its implications for health. These measures can help investigate how stress influences mitochondrial responses across

different cell types and tissues, potentially revealing organ-specific effects akin to mitochondrial diseases. Research in this area aims to elucidate how stress-induced mitochondrial damage, including mtDNA alterations, might biologically embed stressful experiences and affect health outcomes. Longitudinal studies are essential to evaluate the reversibility of stress-induced mitochondrial changes and their impact on overall health. In summary, mitochondria serve as integrators in the stress-disease cascade, bridging psychosocial factors with physiological responses at the cellular and systemic levels. Understanding mitochondrial responses to stress—characterized by dynamic recalibrations and potential for maladaptive changes—provides insights into the mechanisms linking stress with disease processes in the body [80].

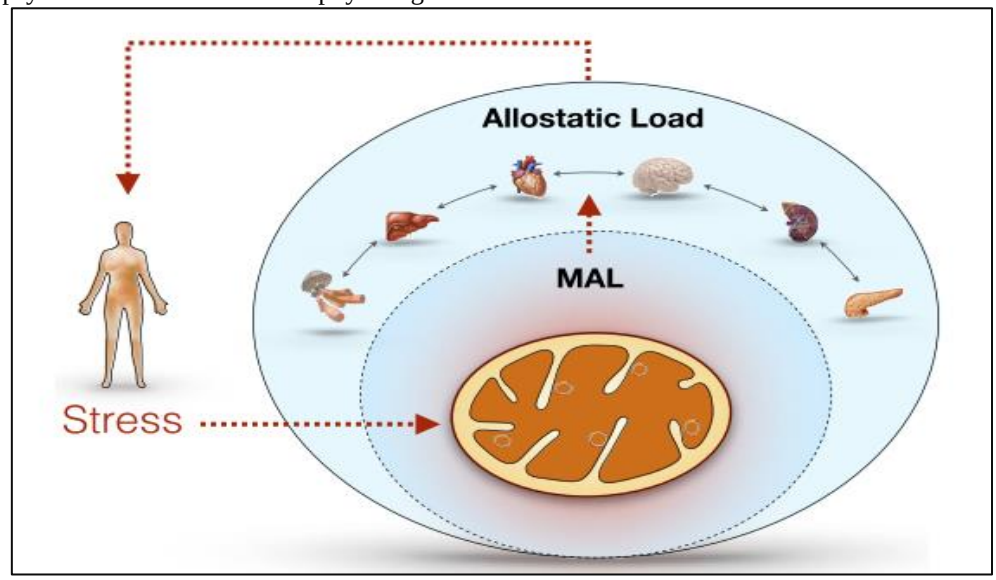

Figure 2: Effect of stress on mitochondria. Mitochondrial allostasis refers to the active process by which mitochondria respond to challenges such as the demand for ATP and other biomolecules, while also providing biochemical signals like limited ROS. Mitochondrial allostatic load (MAL) occurs when mitochondrial functions become dysregulated due to structural and functional changes induced by stressors. This imbalance can lead to impaired cell function, senescence, and cell death over time. Clinical cases of inherited mitochondrial disorders show how mitochondrial dysfunction can affect multiple organ systems. Since mitochondria play a crucial role in systemic allostasis, MAL contributes significantly to overall systemic allostatic load and overload.

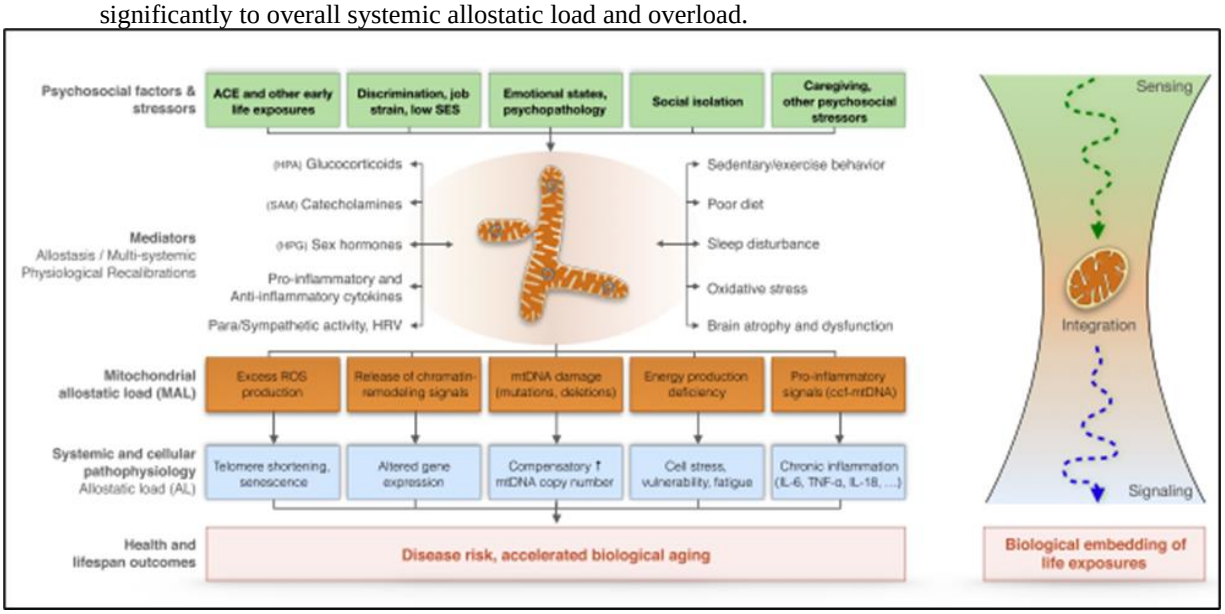

Figure 3: Diseases related to stress impact on mitochondria. Mitochondria play a crucial role in translating psychosocial stress into physiological and cellular changes, contributing to health risks. They interact bidirectionally with stress mediators, leading to mitochondrial allostatic load (MAL). Chronic stress

activates these systems, causing molecular changes that result in systemic pathophysiology and allostatic load (AL). The model suggests that psychosocial stressors induce MAL, which in turn leads to adverse health outcomes. The impact of stress varies depending on the individual's mitochondrial health. Three main hypotheses are: 1) psychosocial factors induce MAL; 2) MAL and mitochondrial defects cause systemic dysregulation; 3) the effects of stress differ based on mitochondrial health.

Effect of Stress on Autonomic Nerves System:

The autonomic nervous system (ANS) plays a critical role in responding to stress and maintaining overall health. It consists of two main branches: the sympathetic nervous system (SNS), responsible for the fight-or-flight response and energy mobilization, and the parasympathetic nervous system (PNS), which promotes rest-and-digest functions and vegetative processes. In a healthy state, these systems are in dynamic balance, with the PNS typically dominating to support recovery and relaxation. Under conditions of chronic stress, however, an imbalance can occur where the SNS remains chronically activated, leading to an excessive wear and tear on physiological systems. This imbalance is often indexed by changes in physiological parameters such as myocardial contractility, peripheral vascular resistance, heart rate (HR), and heart rate variability (HRV). The baroreflex, a mechanism involving pressure-sensitive receptors in the carotid and aortic arches, helps regulate blood pressure (BP) by adjusting sympathetic and parasympathetic outflows in response to changes in BP [81].

Autonomic imbalance, characterized by heightened SNS activity and reduced PNS tone, has been associated with a wide range of mental and physical disorders. These include internalizing disorders (e.g., anxiety, depression), externalizing disorders (e.g., aggression), psychotic disorders, and cardiometabolic diseases such as hypertension, coronary heart disease, and diabetes. The chronic activation of the defense/vigilance response, often associated with perseverative cognition (e.g., worry, rumination), contributes to this autonomic imbalance and is linked to adverse endocrine, cardiovascular, and autonomic outcomes. Historically, several models have been proposed to explain how stress influences physiological responses and health outcomes. The recurrent activation model suggests that repeated stress system activations lead to poor health outcomes. In contrast, the prevailing state model proposes that elevated stress responses persist over time, contributing to chronic health issues. Recent studies also suggest that blunted physiological responses to stress may indicate increased risk for certain health problems [81].

The Generalized Unsafety Theory of Stress (GUTS) integrates these perspectives by positing that the fight-or-flight response is a default state unless overridden by safety signals. Failures to recognize safety signals, rather than ongoing perceptions of threat, may perpetuate chronic stress responses and autonomic imbalance, contributing to long-term health issues. This theory underscores the importance of recognizing and promoting safety to mitigate the physiological effects of chronic stress. Empirical evidence supports these theoretical frameworks, highlighting the association between ANS activity (particularly BP and HRV) and stress-related health outcomes. Further research is needed to validate these concepts and explore effective interventions that can modulate ANS function to improve health in stress-prone populations [81].

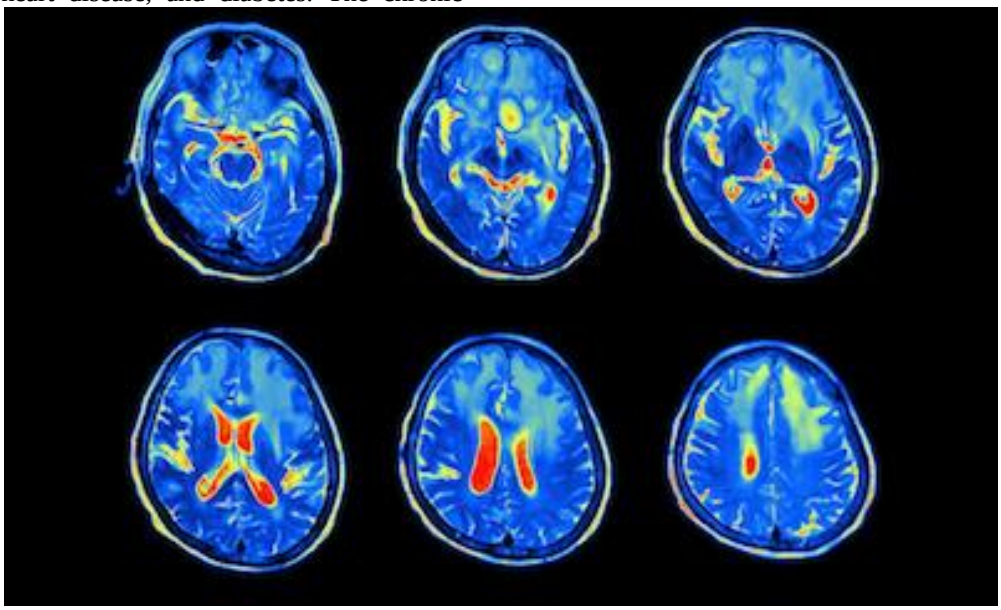

Figure 4: Stress and Autonomic nervous system cells.

Effect of Stress on Memory Cells:

Prolonged exposure to stressful events on a regular basis is known as chronic stress, and it has a major negative impact on mental health, especially on cognitive processes like prospective memory (PM). PM is mostly dependent on brain regions such as the hippocampus and entails remembering to carry out planned actions or intentions in the future. Because of its high concentration of glucocorticoid receptors, which are triggered by stress hormones generated through the hypothalamic-pituitary-adrenocortical (HPA) axis, the hippocampus, a crucial area for memory and learning, is particularly sensitive to chronic stress. Prolonged stress can cause reversible deficits in the shape and function of the hippocampus regions, which impact PM. Chronic stress has been specifically associated with changes in GABAergic inhibition in CA1 and neuronal shrinkage in the CA3 region of the hippocampus, indicating subregion-specific responses to stress. The dentate gyrus (DG), subicular complex (SUBC), and CA1, CA2, and CA3 hippocampus subregions all have different functions in memory processes. For instance, the DG is essential for pattern separation, but CA3 is crucial in encoding new associations. Conversely, SUBC makes it easier to recall previously taught associations. It has been demonstrated that chronic stressors affect various subregions differently, e.g., inducing atrophy in CA3 but not in the DG [82].

Comprehending the impact of chronic stress on PM requires an understanding of these subregion-specific effects. Although more research is needed to determine the precise mechanisms tying chronic stress to hippocampal dysfunction-induced PM impairment, current data points to a complex relationship in which stress-induced alterations in hippocampal structure and function may have varying effects on different types of PM (time-versus event-based). In conclusion, long-term stress has distinct impacts on different hippocampus subregions, which may interfere with their ability to process pain signals. Subsequent investigations focused on clarifying these connections may offer valuable perspectives on remedial approaches to address cognitive deficits linked to prolonged stress [82].

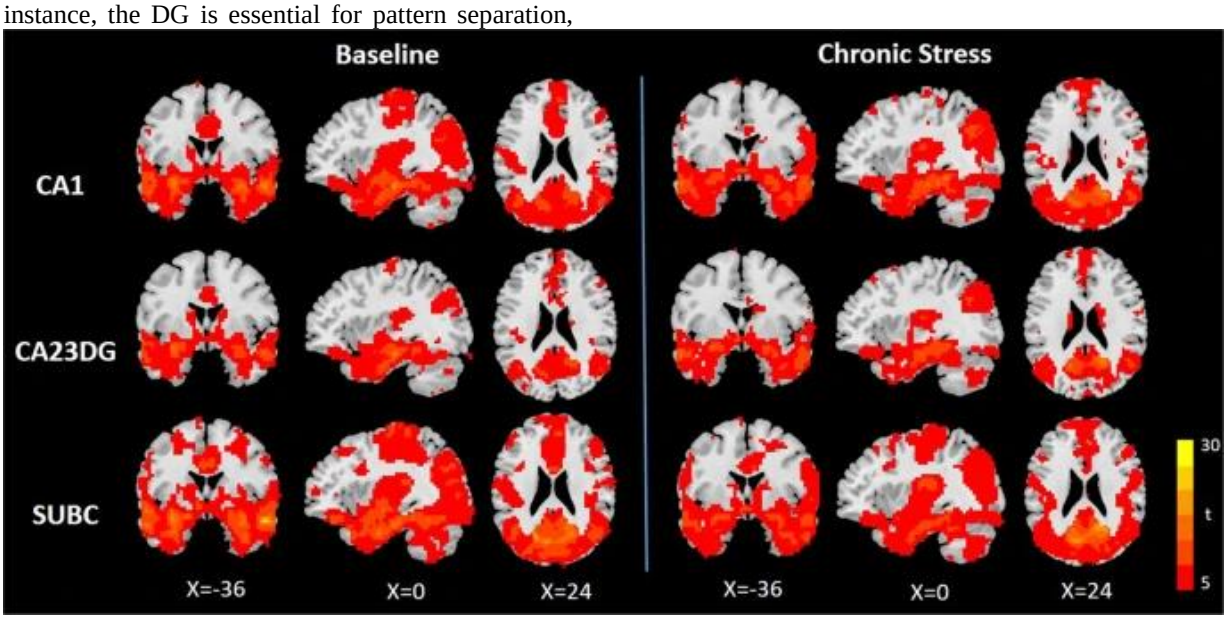

Figure 5: Stress and impact on memory cells. The functional connectivity patterns of hippocampal subregion networks in baseline and chronic stress conditions were analyzed. Statistical significance was set at $p < 0.0001$, corrected using the false discovery rate (FDR). The specific hippocampal subregions examined included Cornu ammonis 1 (CA1), Cornu ammonis 2, 3, and the dentate gyrus (CA23DG), and the subicular complex (SUBC).

Conclusion:

Psychological stress exerts a profound influence on health, affecting both mental and physical well-being through intricate pathways involving the brain, neuroendocrine system, and immune responses. This discussion has highlighted several key themes linking psychological stress to health outcomes, particularly focusing on cognitive functions, cardiovascular health, and the role of the autonomic nervous system (ANS). Firstly, chronic psychological stress significantly impacts cognitive functions, particularly prospective memory (PM), which involves remembering to perform planned actions or intentions. Studies have shown that chronic stress leads to impairments in hippocampal structure and function, affecting memory processes crucial for PM. This underscores the vulnerability of the hippocampus to stress-induced changes, mediated through the dysregulation of glucocorticoids and alterations in neuronal architecture.

Secondly, the cardiovascular system is heavily influenced by psychological stress, manifesting in increased blood pressure (BP) reactivity and impaired heart rate variability (HRV). These physiological responses, driven by the autonomic nervous system (ANS), particularly the sympathetic nervous system (SNS), contribute to allostatic load—a cumulative wear and tear on the body's systems over time. Chronic stress-induced ANS imbalance, where SNS activity predominates over parasympathetic activity, is associated with a range of cardiovascular diseases, including hypertension and coronary heart disease. Moreover, the interplay between psychological stress and the immune system reveals intricate bidirectional relationships. Stress-induced activation of the HPA axis and release of glucocorticoids modulate immune responses, affecting inflammation levels and immune function. This dysregulation can contribute to chronic inflammatory conditions and impair the body's ability to fight infections, highlighting the systemic impact of psychological stress on immune health.

Conceptual models such as the generalized unsafety theory of stress (GUTS) provide frameworks to understand how chronic stress perpetuates physiological dysregulation, suggesting that the failure to recognize safety signals may sustain stress responses and exacerbate health risks. Additionally, the recognition of individual differences in stress responses underscores the complexity of stress-health relationships, emphasizing the need for personalized approaches to stress management and intervention. In conclusion, the evidence presented underscores the pervasive impact of psychological stress on health across multiple domains—cognitive, cardiovascular, and immune. Understanding these mechanisms is crucial for developing targeted interventions that mitigate the adverse effects of chronic stress on health outcomes, promoting resilience and well-being in individuals facing stressful circumstances. Future research should continue to explore these intricate pathways to refine therapeutic strategies and improve health outcomes in stress-related disorders.

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