

RESEARCH ARTICLE

Chronic Stress: The Master Hallmark of Aging

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Abstract

Chronic stress is a pervasive force in modern life, significantly impacting emotional well-being and physical health. This paper explores the profound effects of chronic stress on aging, positioning it as the master hallmark of aging. Chronic stress affects cognitive functioning and is also linked to various physical illnesses, including heart disease, irritable bowel syndrome, chronic fatigue, autoimmune symptoms, and contributing to accelerated aging markers. This paper discusses the central role of chronic stress in the psychoneurobiology of aging and the imbalance between the sympathetic arousal and parasympathetic recovery branches of the nervous system, leading to autonomic dysregulation. This dysregulation causes all systems in the body to work harder, generating more wear and tear and toxic waste products and leading to a breakdown in adaptation. The paper identifies the "Four Horsemen of Chronic Stress"—evolutionary mismatch, developmental lessons from childhood, the stress-success association, and conditioned stressors—as key structural factors driving chronic stress and autonomic imbalance. It also examines the impact of chronic stress on the 12 hallmarks of aging. While not presenting an exhaustive review of all the relevant evidence, this paper is focused on establishing the fundamental role of chronic stress in modulating the process of aging, along with a comprehensive model of resilience that incorporates all factors important in restoring and maintaining organismic balance and optimal adaptability and function.

Introduction

Chronic stress is the inevitable consequence of the growing complexity and uncertainty of modern life, often taking a significant toll on emotional well-being and physical health.¹ Chronic stress plays a critical role in shaping overall health outcomes.

Research evidence shows that chronic stress increases the risk of heart disease, irritable bowel syndrome, chronic fatigue, autoimmune symptoms, PTSD, addiction and other physical illnesses.²⁻⁸ It also impacts emotional regulation and cognitive functioning.⁹⁻¹⁰ There is growing evidence that those who score high on measures related to chronic stress, exhibit accelerated aging markers, such as telomere length¹¹ as well as physiological changes, such as increased insulin resistance.¹²⁻¹³

Aging is the greatest risk factor for disease formation. Chronic stress is as pervasive as poor diet and lack of exercise in our society as risk factors for disease and the aging process. Yet, it has not received sufficient attention in the longevity conversation.

Much of longevity research, medications, supplements and treatments involve repairing damage or restoring loss of function or balance, in one or more biological system. Chronic stress leads to the dysregulation of the autonomic nervous system. It is the most significant factor causing dyspnoea, a condition involving the misuse or misdirected expenditure of energy leading to cellular damage, loss of function and contributing to the disease process.¹⁴⁻¹⁵ The greater the autonomic dysregulation, the harder the body works, causing increased toxic waste production, and greater wear and tear on all bodily systems.

The analogy is of a car that's out of tune. With each additional stress the equivalent of the car going up a hill. The car will have less power, generate less energy, waste more gas, produce more toxic exhaust, and add friction that ultimately causes extra wear and tear on all parts of the car. Thus, any conversation about longevity should begin with chronic stress, which has the greatest impact on all systems in the body and thus the 12 hallmarks of aging. For this reason, I have labelled chronic stress as the master hallmark of aging.

This article will show the links between chronic stress and all the hallmarks of aging and identify the mechanisms of this effect. But first I will discuss structural vulnerabilities, what I call "The 4 Horsemen of Chronic Stress". These are the issues that bias one towards chronic stress and autonomic imbalance, freeze the ability to adapt, and create resistance to addressing the imbalance. The paper concludes by describing a model of resilience designed to reverse this process and regain optimal adaptability.

Chronic stress is a destructive and constant life factor

The four horsemen of chronic stress

The stress response we employ as adults does not fit the environment we live in! Instincts that should protect and sustain, can do the opposite. In addition, the instinctual and unconscious mechanism of conditioning for survival, frequently works against us.

The ultimate consequence of chronic stress is that its impact has a magnifying effect, whereby impairment of organ and function render one less capable of withstanding new stresses. For example, chronic stress impairs the functioning of the hippocampus. One role of this important nuclei in the brain is to modulate and dampen the stress response. As the brain engages the stress response, the hippocampus applies a braking action to turn down the sympathetic activation. With chronic stress, that function becomes impaired. In fact, chronic stress shrinks the hippocampus and has been shown to induce dendritic atrophy and debranching in its CA3 pyramidal neurons. The result is less dampening of the stress response and greater dysregulation.¹⁶⁻¹⁷

First Horseman: Evolutionary mismatch of the survival-threat response

The human stress response evolved over hundreds of thousands of years to fit our species to its environment. The result of that process was the development of the fight or flight response to survive danger and threat. When our ancestors were chased by either an animal or a hostile human, their survival depended on how well they ran away, or fought. And most threats were true, life-threatening dangers. There was little gray area such as a small threat. One size response that fits all was an appropriate adaptive design.

Today, few if any of the myriad daily stressors can be effectively addressed with either fighting or running from them. Not only is there a mismatch in which far more energy is utilized than a situation requires, but then additional energy is required, along with the accompanying tension to hold that mobilization in check.

Next, the fight or flight survival mechanism was designed through evolution to be used sparingly, probably not more than once each day, and on many days, not at all. If we look at the modern person's typical day, there are stresses occurring frequently and often continuously. Conversely, how many symbols or cues indicating safety does one experience during a typical day, that allows a shift into recovery mode? Thus, there is a continuous mobilization of the stress response with little shifting into recovery, to

restore the resources that were used up, to minimize toxic effects of overuse of biological resources and to regain balance.

By having this mismatch between the stress response and the environment in which it's deployed, there is a structural vulnerability to autonomic dysregulation, and dysponesis.

Second Horseman: Developmental mismatch: imprinted lessons from childhood

In addition to an evolutionary mismatch, there is a developmental mismatch between the environment in which we learn how the world works, how to survive and how to use the stress response, and our adult environment in which we deploy this stress response. Childhood is the most impactful period in which lessons of life takes place. That's because early learning is survival learning. Where can I expect the food to be and what do I have to do to get it? As a dependent organism the next unconscious question is who is making the food available, and who is protecting me and keeping a roof over my head? Who does my survival depend upon?

As a result, we become tuned to our primary caregivers. In fact, our nervous system develops in synchrony with these caregivers¹⁸. We depend on them to meet our needs. We learn lessons of what they like and what they don't like. We adjust and model their behaviors and thinking. When the child's needs are not met, it has an emotional impact that leaves scars or wounds. These wounds to our identity and unmet needs will unconsciously drive and motivate adult behavior and establish biases that interfere with our objectivity. Threat evaluation – what is dangerous - is not objective. The lessons of childhood frequently result in an over-assessment of danger and threat. In other words, the childhood environment often leads to negative expectations and a bias towards overuse of the stress response, while interfering with parasympathetic recovery from the stress response. Research has found that while stress reduces neuronal arborization in the hippocampus it increases in the amygdala, where threat and danger perception occurs.¹⁷ Furthermore, unconscious messages from one's parents and environment can result in low self-esteem. This translates into experiencing a greater level of danger in the world and the more frequent triggering of the stress response.

Third Horseman: The stress and success connection

The one thing that most successes have in common is stress. For example, an important exam, a big presentation, or a task to complete under time pressure, are all stressful situations that can lead to success. Donald Hebb, a pioneer of neurosciences said, "Neurons that fire together, wire together".¹⁹ Our brains have wired stress and success together due to their occurring, so frequently at the same time.

In other words, these successes cause us to unconsciously seek out stressful behaviors. And this is also one of the reasons we all resist "managing" stress – because of this association between stress and success.

The stress response itself is not the culprit of dysregulation. It's the continual activation of the stress response - chronic stress - that one doesn't recover from. Going from one stress to the next throughout the day without recovery. Figure 1 shows the relationship between arousal – the stress response - and both performance and health. You will note that there is a range of stress activation I refer to as your stress sweet spot, where performance and health are at their highest levels. And we all have this window of optimal functioning before stress turns into strain, wear and tear and then burn out.

Now notice that there are two curves, "A" and "B". The curve "B" is achieved when one has developed greater resilience. In my book, *The 9 pillars of resilience: The proven path to master stress, slow aging, and increase vitality*,²⁰ I propose that when you optimize for these 9 principles of resilience, you shift the stress – performance curve to the right – curve B. In other words, the more resilient you are, the greater the amount of stress and strain you can endure - a larger sweet spot - before a deterioration of either your performance or your health. Furthermore, note that at the optimal levels of activation, resilient people are able to raise peak performance under higher levels of pressure or stress. They are able to handle pressure better.

Fourth horseman: Conditioned stress

Here again survival mechanisms interfere with optimal adaptability. Modern life with its complexity, and uncertainty and where getting closure is usually a long-term process, also results in countless environmental stimuli becoming associated with stress. A simple example is getting bills in the mail. Each bill may contribute to getting tense when the mail arrives. There are countless opportunities for aspects of your environment to be associated with and thus conditioned to either danger or the stress response and expectation of stress. Therefore, the frequency of stresses in our lives create innumerable and invisible conditioned triggers for the stress response.

If you head off to work and worry that something will go wrong; something you did, or will do, might be judged, walking out the door can automatically trigger stress, whether there is any real danger or not. Since this occurs automatically, outside your awareness, you may never consider addressing this driver of imbalance.

This conditioning effect can result in another common form of learning and behaviors. If you have something coming up

that's important to you and you become anxious about how this will turn out. And you are anxious for a few days, perhaps getting poor sleep the night before. The event takes place, and you do well. What is the takeaway? Instead of it being, "I guess I don't have to worry or be anxious the next time", again, the pairing of anxiety and success frequently results in the unconscious message, "when I worry and am anxious, I do well." This isn't a conscious decision, but again, neurons that fire together wire together. In other words, the conditioning process perpetuates worry and anxiety. And thus, chronic stress.

Resistance to Restoring Balance

The 4 Horsemen of chronic stress gives an indication as to why people have difficulty engaging in a process, such as stress management, to restore autonomic balance and healthy adaptability.

The 12 Hallmarks of Aging

Aging is characterized by several biological changes, often referred to as the hallmarks of aging. These commonly identified 12 hallmarks, with considerable overlap, include altered intercellular communication, cellular senescence, chronic inflammation, deregulated nutrient-sensing pathways, impaired autophagy, dysbiosis, epigenetic alterations, genomic instability, loss of proteostasis, mitochondrial dysfunction, stem cell exhaustion, and telomere attrition. Each of these hallmarks contributes to the aging process. The process of enhancing longevity usually involves methodology that impacts one or more of these hallmarks.

However, there is one thing all 12 have in common. Each is negatively influenced by chronic stress. Therefore, if you are interested in slowing the aging process, you must address this important modulator of all 12 hallmarks. One can focus on a specific illness and attempt to reduce its prevalence and intensity, but if you address chronic stress, this reduces the probability of developing almost any symptom, while maintaining health and increasing health span. In this section I'll identify the 12 hallmarks of aging and how each is impacted by chronic stress.

1. Altered Intercellular Communication

Altered intercellular communication is a characteristic of aging that affects various physiological processes, such as immune response and hormonal regulation.²¹ Chronic stress disrupts cell communication between neurons by altering neurotransmitter levels, including GABA, dopamine, norepinephrine, serotonin, and melatonin.²² This disruption can lead to down-regulation of 5-HT1A receptors in the brain, affecting regions like the hippocampus and cortex.²³ Chronic

stress-induced changes in neurotransmitter levels can contribute to neurodegenerative diseases such as Parkinson's disease, which is characterized by the degeneration of dopaminergic neurons.²⁴

2. Cellular Senescence

Cellular senescence is characterized by the cessation of cell division and the secretion of proinflammatory molecules, arising from factors such as DNA damage, oxidative stress, and mutations. Chronic stress is associated with increased expression of senescence markers like p16 and p53. Studies have shown that chronic stress exposure, perceived stress, and accumulated daily stress appraisals are linked to higher expression of the p16INK4a-encoding gene CDKN2A in leukocytes.²⁵ Experimental studies in mice have demonstrated that chronic stress increases p53 and p16INK4a expression in the liver, spleen, and bone marrow leukocytes.²⁶

3. Chronic Inflammation

Chronic inflammation, or "inflammaging," is a key component of the aging process and is closely related to the accumulation of senescent cells and infectious pathogens. Chronic stress disturbs the balance of the immune system, inducing both peripheral and central inflammation.²⁷ While acute stressors may enhance immune function, chronic stressors suppress it, leading to an over-activated immune system and an imbalance between pro-inflammatory and anti-inflammatory mechanisms.²⁸ This imbalance contributes to neuroinflammation and various age-related diseases.

4. Deregulated Nutrient-Sensing Pathways

Deregulated nutrient-sensing pathways plays a crucial role in the development of age-related metabolic disorders and contributes to the decline in overall health with increasing age. Chronic stress, particularly early-life stress, affects hypothalamic nutrient sensing pathways.²⁹ Studies in mice have shown that early stress exposure leads to lower expression of genes critical for nutrient sensing, such as *Lepr*, and reduced circulating leptin levels.³⁰ These changes can have long-term effects on metabolic health and aging.

5. Impaired Autophagy

Impaired autophagy is another hallmark of aging, characterized by the accumulation of dysfunctional components within cells due to the reduced ability to remove damaged organelles and proteins. Chronic stress disrupts neurogenesis, a process regulated by autophagy and is a risk factor for neuropsychiatric disorders.³¹

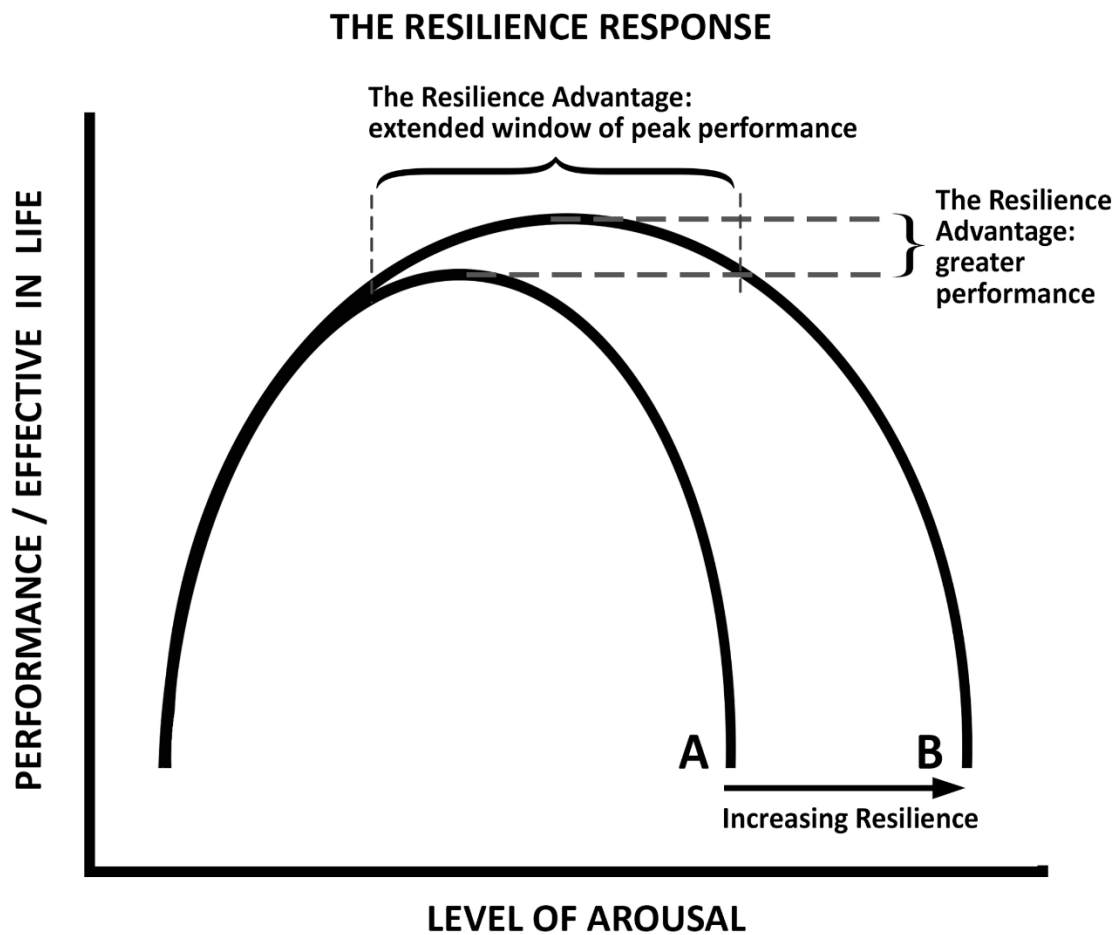


Figure 1. Stress activation – performance curve, showing how resilience mitigates impact of chronic stress and produces a larger stress sweet spot.

Activating autophagy can increase neurogenesis and counter the detrimental effects of chronic stress, making autophagy-activating molecules promising candidates for combating stress-related disorders.³²

6. Dysbiosis

Dysbiosis refers to an imbalance in the gut microbiome composition and function, which is associated with various pathological conditions and overall health.³³ Chronic stress promotes gut bacterial imbalances, lowers diversity, and reshapes the gut bacteria's composition through stress hormones, inflammation, and autonomic alterations.³⁴⁻³⁵ This dysbiosis can alter eating behavior, mood, and increase the risk for depression.

7. Epigenetic Alterations

Epigenetic alterations contribute to age-related changes in gene expression and overall epigenomic dysregulation.³⁶ Chronic stress can modify DNA methylation, leading to altered gene expression and disease phenotypes. Early-life stress, such as childhood abuse, has lasting effects on DNA methylation that persists into adulthood.³⁷ These epigenetic changes can contribute to the development of age-related diseases and accelerated aging.

8. Genomic Instability

Genomic instability is characterized by the accumulation of mutations in DNA, contributing to aging.³⁸ Chronic stress produces epinephrine and norepinephrine, which can bind to cells and induce DNA damage. Long-term exposure to these stress hormones results in significant increases in DNA damage, leading to mutations and an increased potential for cellular transformation and tumor progression.³⁹ This genomic instability accelerates the aging process and increases vulnerability to cancer.

9. Loss of Proteostasis

The loss of proteostasis involves the accumulation of misfolded proteins and impaired protein degradation, leading to detrimental effects on cellular function and age-related diseases.⁴⁰ Chronic stress affects total serum protein patterns and can lead to measurable changes in serum protein levels.⁴¹ Stress and stress hormones have been implicated in stress-induced tau phosphorylation and beta-amyloid production, which are associated with neurodegenerative diseases like Alzheimer's.⁴²

10. Mitochondrial Dysfunction

Mitochondrial dysfunction is a hallmark of aging, characterized by impaired energy production and various

cellular processes due to accumulated DNA mutations and oxidative damage.⁴³ Chronic stress influences mitochondrial biology, leading to decreased energy production capacity and altered mitochondrial morphology.⁴⁴ These changes contribute to the decline in cellular function and overall health with age. It might also play a role in fatigue, usually associated with chronic stress.

11. Stem Cell Exhaustion

Stem cell exhaustion is characterized by a decline in the number and regenerative capacity of stem cells with age.⁴⁵ Chronic stress impacts the number and function of hematopoietic stem cells (HSCs), leading to decreased HSC function and exhaustion.⁴⁶ Chronic stress-induced proliferation of HSCs results in extensive release of inflammatory leukocytes into circulation, promoting plaque inflammation and contributing to age-related diseases.⁴⁷

12. Telomere Attrition

Telomere attrition is driven by the gradual shortening of protective caps on chromosome ends with each cell division, leading to cellular senescence.⁴⁸ Chronic psychological stress has been shown to cause telomere damage and shortening.⁴⁹ Experimental studies in animals and human longitudinal studies have demonstrated that stress-induced telomere shortening is a significant pathway through which chronic stress accelerates aging.⁴⁹

A methodology for developing greater resilience, and restoring optimal adaptability to slow aging: The 9 pillars of resilience

As a result of people's resistance to addressing chronic stress it's important to make it clear, not all stress is bad. By acknowledging this fact, it highlights the internal conflicts experienced around managing stress. These conflicts have been highlighted in the section on "The Four Horseman of Chronic Stress". Therefore, I have redefined the stress response as an important tool for performance and success. But the key is to find your stress sweet spot, that level of stress that maximizes your performance and life satisfaction, while helping you stay in that place of optimal balance, recovery and health. The second re-definition is that resilience should no longer be defined as the ability to bounce back, where you keep making the same mistakes, and engage in outmoded conditioned patterns that drive mind/body imbalance. Instead, true resilience is the ability to bounce forward, where we learn to break free of the messages and lessons of childhood that not only scar, but also gives one an identity that locks in the old patterns. By breaking away from these constraints we free ourselves to regain optimal adaptability.

Pillar 1: Relationship with self

Perhaps the pillar that all others rest on, this is about how you feel about yourself and how you treat yourself. It is important to treat yourself with: respect, love, compassion, support, acceptance and care. Despite childhood lessons, it's never constructive to put yourself down, or be hard on yourself. It only creates more tension and undermines confidence. This pillar is about recognizing the harm created by being judgmental, critical and negative towards yourself, while developing a healthy internal voice.

Pillar 2: Relationship with others

This is the ability to communicate and establish close and intimate relationships, and to receive support. Friends and other relationships in which positive affect is expressed, enhances the sense of a safe world. Relationships can serve to validate and reinforce a sense of being okay. This impacts confidence and personal capacity. The ability to be intimate facilitates a physical opening that enhances the flow of energy in your body. At the same time this pillar is about setting appropriate boundaries, so you are not hurt by the negativity and toxic energy of others.

Pillar 3: Relationship with something greater

This can have a spiritual emphasis, or it can be your involvement with community, charity or other forms of service. Connection, meaning and belief in something greater than yourself, can include purpose, and makes daily hassles less significant. It enhances a sense of security and hope. It takes the focus away from your problems. Perhaps most important, it lessens the sense of isolation and alienation, while giving your life meaning and direction. All these factors reduce uncertainty, a major source of stress.

Pillar 4: Physical balance and mastery

This is the ability to deeply relax and to quickly recover from stress. It is being able to keep your stress response in proportion to the demands of the specific situation and not over-react. And to fully utilize sleep for optimal recuperation. It's practicing a regular relaxation practice to balance the frequently utilized stress response.

Pillar 5: Mental balance and mastery

This pillar begins with a growth mindset, in which a weakness is experienced as a challenge and area to improve upon. It's about having a positive attitude and positive expectations. It is also the ability to control your thoughts; to let go of thoughts and worry and move on, as well as to be focused and avoid distractions.

Pillar 6: Emotional balance and mastery

Unexpressed emotions or emotions that you are unaware of, make you more sensitive to hurts and to inappropriate over reactions. They are accompanied by physical holding patterns, anxiety, and stress. This component involves awareness of one's feelings, the ability to appropriately express these emotions, and then the ability to let go and thus not carry around excess baggage or unfinished business. Emotional wounds that are not addressed can unconsciously drive behavior that is counter-productive and contribute to various symptoms.

Pillar 7: Presence

This component is about being fully in the moment, aware and in contact with your environment, and not distracted by thoughts, worry or other preoccupations. It is also about the quality of the energy that you project out into the world and how well you are received by others.

Pillar 8: Flexibility

This is the ability to adapt to changing circumstances that minimizes frustration, anger and tension. This enhances your ability make adjustments to better achieve your goals. It also includes flexibility in your perception of the world, including putting yourself in someone else's shoes. It is the ability to learn and adjust from experience.

Pillar 9: Power

I define this as your ability to get things done. This includes courage to take action, persistence in the face of obstacles and frustration, focus in keeping the goal in view, and assertiveness in making your desires known. It also involves the ability to make decisions as well as planning and being strategic. This component enhances your sense of control, self-trust and confidence.

Conclusion

In this article I have identified chronic stress as the defining and master hallmark of aging. Its pervasiveness in our lives, along with what I have called "The 4 horsemen of chronic stress", creates the conditions under which we are all susceptible to driving autonomic dysregulation. I have shown how this dysregulation leads to a negative impact on all 12 identified hallmarks of aging. In the final section I have presented a new definition and model of resilience that can help reestablish optimal adaptability, organismic balance while slowing aging.

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Conflicts of Interest

The author declares no conflict of interest.

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