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Review

The geroscience agenda: Toxic stress, hormetic stress, and the rate of aging

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ABSTRACT

Geroscience offers a counterpoint to the challenged pursuit of curing diseases of aging, by focusing on slowing the biological aging process for extended healthspan earlier in life. Remarkable progress has led this field toward animal trials and the next challenge lies with translation to humans. There is an emerging number of small human trials that can take advantage of new models integrating behavioral and social factors. Understanding dynamic aging mechanisms, given the powerful social determinants of aging (Crimmins, 2020) and human variability and environmental contexts (Moffitt, 2020), will be critical**. Behavioral and social factors are intrinsic to aging. Toxic stressors** broadly defined can lead to **stress-acceleration of aging**, either directly impacting aging processes or by shaping poor behavioral health, and underlie the socioeconomic disparities of aging. In contrast, **hormetic stressors**, acute intermittent stressors of moderate intensity, can produce **stress resilience**, the ability for quick recovery and possibly rejuvenation of cells and tissues. Although health research usually examines static biomarkers, aging is reflected in dynamic ability to recover from challenges pointing to new interventions and targets for examining mechanisms. A fuller model incorporating stress resilience provides innovative biobehavioral interventions, both for bolstering response to challenges, such as COVID-19, and for improving healthspan.

1. Introduction

1.1. Geroscience meets social and behavioral research

There has been a recent paradigm shift away from attempting to cure specific diseases, the "whack-a-mole" approach, to that of understanding and slowing biological aging – the underlying cause of diseases of aging – as embraced by the emerging interdisciplinary field of **Geroscience**. To reduce the burden of disease and improve the number of years of healthy living, **healthspan**, we must slow the biological process of aging. This would have a large impact on both the cost of medical care, and on population health (Austad, 2016). For example, slowing aging and thus onset of dementia by two years will reduce the number with dementia by 2.2 million (Zissimopoulos et al., 2018). Slowing aging will save seven trillion dollars in 50 years (Goldman et al., 2013).

Remarkable progress has led toward trials in animal species. The NIH Intervention Testing Program (ITP) has tested promising compounds in three different labs for replicability, and several compounds, such as rapaymycin, appear to slow aging in both male and female mice, as reviewed elsewhere (Austad, 2016). There are several human trials underway, such as those testing metformin's ability to prevent multiple disease outcomes (Barzilai, 2017) and testing rapamycin's ability to reduce functional signs of aging (Kraig et al., 2018), in addition to studies of caloric restriction (e.g., Belsky et al., 2017b).

However, formidable challenges lie ahead with translation to humans, in their natural contexts as social mammals. In the next generation of aging research, understanding the dynamic aging mechanisms in humans, given human variability, culture, and environmental contexts, will be critical (Moffitt, 2020). Behavioral and social research offers an important view into aging mechanisms that can be incorporated into translational geroscience. Many of the causal social-behavioral mechanisms influencing healthspan have long been identified. As Crimmins describes in this issue (Crimmins, 2020), the early fundamental social causes of disease can be referred to as the **social hallmarks of aging,** including low socioeconomic status and minority status, adverse life events, poor health behaviors, and poor mental health. While chronological age will always be the most important fixed predictor of disease onset, in humans one of the largest factors explaining variation in patterns of disease is one's socio-economic status, at least in western countries. One's income or education predicts timing of morbidity and mortality in the U.S. (Adler et al., 1993). Much evidence suggests that socio-economic status serves as a proxy factor that shapes a multitude of early influences,

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not just material deprivation and poor health behaviors, but also promoting chronic social threat stress which can directly influence aging trajectories (see Section 6).

1.2. Foundations of stress and aging: from social hallmarks to stress processes

Psychological threat stress underlies the social hallmarks of aging. To understand how stress impacts aging, we must go beyond the global concept of stress, and dive into the refined study of stressors and stress responses (Epel et al., 2018; See Stress Typology Appendix). The study of stress must use precise definitions of its essential components. The external exposures, "**stressors**," can be physiological stressors (e.g., surgery, heat, hypoxia), the focus of basic geroscience research, or, more common to social sciences, stressful events or ongoing difficult situations (eg, divorce, job loss, caregiving). Both physiological and psychological stressors can be viewed and tested through a similar framework—as both can potentially lead to adaptive salutary changes (hormesis) or accelerated aging, depending on the nature of the stressors and of the stress response.

The **stress response** includes the psychological and physiological responses to stressors. The acute stress response is essential for healthy functioning, but the combination of exposure to a chronic stressor, and a chronically mounted psychological threat stress response without the perceived resources to cope has the potential to alter the hallmarks of aging. This is referred to as **toxic stress**.

Acute vs. chronic physiological stress as determinants of aging. The qualities of a stressor drive a biphasic response. This is a fundamental principle which comes from both physiology ("hormesis") and psychology ("the Yerkes-Dodson law") (Calabrese, 2008). Brief intermittent, low dose stressors can lead to positive biological responses, improving resistance to damage, which is called **hormesis**. In contrast, a high dose and chronic exposure can override these mechanisms, resulting in damage or death. Hormesis is the set of evolutionary well-preserved mechanisms of biological plasticity to survive and thrive when exposed to harsh circumstances and substances. Hormesis traditionally described a cell's or organism's bi-phasic response to an external chemical or stressor. There is indeed overlap between stress processes and aging processes, and the two become intertwined with the concept of hormesis.

Toxic stress includes traumatic or ongoing adversity for months on end, and the psychological responses– chronic high perceived stress, burnout, or depression. Many large scale studies demonstrate that traumatic or chronic psychosocial adversity, including low socioeconomic status, predicts higher allostatic load, whereas high levels of psychosocial resources are associated with lower allostatic load, with small but reliable effects (Danese and McEwen, 2012; Wiley et al., 2017), described further under "reserve capacity" (Section 4).

From Homeostasis to Allostatic Load. Stress research started with examination of the stress responses to acute stressors in rodents. Cannon's stress studies led to the popular concept of homeostasis (Cannon, 1932) but a simple linear model of homeostasis does not explain the range of human stress responses, and there have been many elaborations of this concept. Selye described the continuum from acute stress to chronic stress (Selye, 1956). Acute stress can be hormetic when there is quick recovery back to homeostasis. Given the complexity of physiological regulation, and that our body mounts a response in mere anticipation of threat, Sterling and colleagues have described allostasis as a more encompassing description of the body's regulation– the constant fluctuations to meet expected demands (Schulkin and Sterling, 2019) which in biogerontology has been called "homeodynamics." Chronicity of stressor exposure reveals a "*fragility in homeostasis*" (Ramsay and Woods, 2014) when physiological signs of 'exhaustion' appear, such as, in rodents, damage in organs. McEwen and colleagues have labeled this cost of adaptation–the dysregulation and damage across systems–as **allostatic load** (McEwen, 2004).

The concept of allostatic load, whether it is at a systemic or cellular level, gives us an intermediate phenotype of aging, an early step toward development of diagnosable disease. This is a critical concept in geroscience, and in fact many of the actual measures of allostatic load used in the psychology and public health literature are actually also indices of aging (Entringer and Epel, 2020). Geroscience leaders have started to identify the biomarkers important in geroscience trials, as those that can predict aging outcomes and mortality, and are responsive to interventions, and this short list so far includes glucose control and inflammation (Justice et al., 2018). Thus, there is potentially great overlap between geroscience biomarkers and the stress-related allostatic load markers described in Section 3 (cellular, multi-system, and measures of recovery). It is clear these fields can inform each other and should be more integrated going forward.

2. An integrative model of stress and aging. Stress acceleration (toxic stress) and stress rejuvenescence (hormetic stress)

Given the important role of social stress in aging, we need a deeper understanding of types of stress exposures. An overarching model explains the range of stress exposures, from toxic stress to acute hormetic stress, and our body's diverging responses to these exposures**. Our stress responses are not typically thought of as basic mechanisms of aging but indeed they are actively shaping rate of aging.**

As shown in Fig. 1, the dose and intensity of the stressor determines in part whether the organism responds with positive physiological changes or impairments in aging processes (modified from Franceschi et al., 2018). The exact timing of stressor exposure is an important determinant of a hormetic or pre-conditioning effect, as some stressors lead to sensitization across stressors, rather than habituation (i.e., Belda et al., 2016) and this may differ by species, stage of development, and stressor paradigm. Therefore, a general model cannot determine the exact parameters of intensity and dose for hormetic stressors. It is an important area of future research to identify the boundary conditions and inflection points for the range of potentially hormetic stressors (Epel and Lithgow, 2014). Moderate stressor exposure can lead to both housecleaning in the cells, making them appear younger or rejuvenated, as well as growth of new neural pathways. Over time, the accumulation of hormetic stress can promote slowing of aging processes.

2.1. Hormesis is a form of stress resilience

This paper brings together the hormesis literature with the broader stress resilience literature. The cellular biology of hormetic responses is well mapped, characterized by some general common responses as well as stressor specific responses. The acute stress response has a common pathway of creating calcium influx, oxidative stress, and energetic stress. This increases transcription factors such as NRF-2, FOXOS, CREB, and NF-KB, leading to many hormetic effectors, such as chaperone proteins (eg, heat shock proteins which help fold proteins efficiently and prevent protein aggregation), ER stress, endogenous antioxidants (SOD, Glutathione), growth factors, and mitochondrial proteins (Mattson, 2008a). After moderate doses, the cells become resistant to many other types of stressors (heat, UV, oxidative stress, metals), and to resistant to death (Murakami et al., 2003).

Hormesis is a universally observed phenomena across many types of cells and types of stressors, including psychological stress. In model organisms, short manageable stressors lead to improvements in aging, although this depends on types of stressor and species (Lagisz et al., 2013; Rattan, 2008). For example, low dose gamma radiation over time can extend average lifespan up to 30% in mouse studies (Calabrese and Baldwin, 2000).

In humans, there is evidence of hormetic stress, such as the effects of exercise, although this is not typically *labeled* as hormesis. Hormesis naturally applies to humans– not just to cells but to physiological and psychological regulation. A typical example is vaccination –which leads

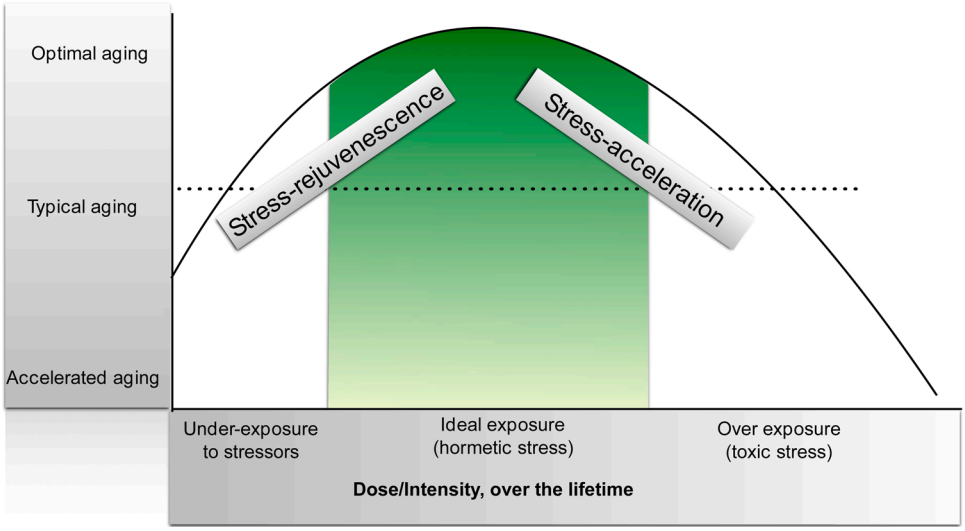

Fig. 1. Lifespan stress exposure shapes rate of biological aging.
This model can apply to psychological stressors and physiological stressors like exercise. In terms of psychological stressors, **under-exposure** to the typical daily and major life events can lead to lack of development of stress buffering resources, and poor ability to quickly recover from stressors. Biologically the lack of acute stressors prevents the intermittent episodes of cellular 'housecleaning' activities that slow aging. **Ideal exposure** to sufficient numbers of manageable challenges throughout life stimulate cognitive growth, coping skills, and emotion regulation skills, as well as the need for supportive social networks. Biologically, ideal exposure to acute stress can have hormetic effects, leading to rejuvenescence—functioning that is enhanced (or "younger") compared to baseline. **Over-exposure** to stress without sufficient resources (toxic stress) can lead to maladaptive neural pathways of overresponding to stress, depression, and stress related acceleration of aging from cells to regulatory systems. This figure is adapted from Franceschi et al. (2018).

to enhanced immune responses later. Here we expand the definition of hormetic stress to include the positive stressors that humans engage in—such as short term stressors like exercise and temperature stress, but also novel challenging experiences that expand coping resources, knowledge, generativity, and feelings of accomplishment, described further below (Section 2.2).

Since hormetic stress has traditionally been applied to cellular physiology, we use the larger concept of '**stress resilience'** as the widest umbrella term for describing when humans recover quickly, in any system, from various exposures. As shown in the Appendix, there are many overlapping terms that relate to the concept of stress resilience. Just as the term "stress" is a multi-level construct that needs to be examined in a sophisticated interdisciplinary manner, stress resilience is also a multi-level construct that encompasses the full range of human exposures, responses, and inter-related systems. The term stress resilience thus subsumes the concepts of psychological resilience, physiological resilience/enhanced allostasis, and social resilience. This model of stress resilience can thus be applied to most processes– at the cellular level, physiological level, and psychosocial level.

2.2. *Psychosocial stress resilience*

Psychosocial stress resilience here refers to the dynamic recovery in psychological, behavioral and social processes and related physiological processes in response to psychosocial stressors. High psychosocial stress resilience is reflected by quick physiological and affective recovery. The neurochemistry of psychosocial resilience has been described, based on rodent models (Cathomas et al., 2019).

Whether a stressor leads to a hormetic or toxic response is not solely determined by the chronicity and severity of the stressor. It is also determined in part by the psychological appraisals, which are shaped by the context, culture, personal history and personality of the individual. When one feels demands exceed resources, in any situation, which we label as threat stress, this can create a physiological and emotional stress response (Folkman et al., 1986). Repeated threat stress response over time will last longer and be more wearing. In contrast, if they view it as a positive challenge that they have the resources for, they will have a profile of quicker recovery, as summarized elsewhere (Epel et al., 2018). Thus the appraisal of the stressor, along with the chronicity, co-determines the physiological response.

It is not just stress responses to major events that matter. Our frequent daily stress responses have cumulative effects: The tendency to have slower recovery of negative mood or greater loss of positive mood after a daily stressor predicts inflammation and long term disease and mortality (Charles et al., 2013; Mroczek et al., 2015; Piazza et al., 2013; Sin et al., 2015).

Short term manageable stressors, such as physical or cognitive challenge that can promote growth, learning and development can lead to protective responses. An example of this is found in studies of the Experience Corps. Exposing elderly retired people who are often isolated to a job mentoring at-risk youth in schools is often viewed as stressful but leads to feeling more purpose in life. In men, it has been linked to better health and increases in hippocampal volume (Carlson et al., 2015; Gruenewald et al., 2015; Varma et al., 2015).

In the case of coping with chronic stressors, most people (around 80%) recover to baseline levels of well being after a loss or disaster (Galatzer-Levy et al., 2018). Resilience may develop over time, leading to more mastery, purpose, faith, self esteem, and thus more resilient responses to future stressors.

In contrast, toxic exposures accumulate over a lifetime, promoting "**stress-acceleration of aging**" processes (see Fig. 1). Toxic exposures come in many forms: Chronic stressors for decades, multiple shorter term exposures over years, and stressors embedded early in life, can all have toxic effects when there are insufficient resources to cope, and no opportunities to fully recover.

2.3. *Lifespan Matters*

Developmental factors are critical for understanding when stressors can be hormetic vs. toxic. We do not know precise developmental trajectories for differential effects of toxic stress on mental and physical health and even less is known about hormesis across the human lifespan. With aging, there is a decrease in both the reproductive and anabolic hormones that are part of a salutary acute stress response (Epel et al., 1998), and a reduction in aspects of molecular hormesis, such as a lower heat shock response to stressors (Calabrese et al., 2014; Epel, 2008). We know most about the developmental impact of toxic stressors. While there are myriad individual patterns of exposures, traumatic stress or material deprivation have larger effects early in life than when they occur at later periods; Early life adversity is predictive of a range of poor

outcomes, including poor mental health, health behaviors, biomarkers of aging, and earlier disease onset (Deighton et al., 2018; Hughes et al., 2017) although plasticity is still possible (McEwen and Morrison, 2013). Given the sensitive period of pregnancy, it is not surprising there is evidence of transgenerational effects of stress and pregnancy complications on systems regulating aging such as telomeres and epigenetics (Epel, 2020; Girchenko et al., 2017; Ross et al., 2020).

A careful meta-analysis of the effects of early adversity points to psychological threat stress, rather than material deprivation, as the factor underlying accelerated biological aging such as early puberty, telomere shortening, and brain development (Colich et al., 2020). For trauma and abuse, the earlier in life, prenatal and pre-pubertal, when the brain is most rapidly developing, the larger the imprint of lifelong effects on mental and physical health (Agorastos et al., 2018). There are many examples of early adversity with accelerated biomarkers of aging in children: In prepubertal children, early life adversity leads to greater inflammatory acute stress response, and basal inflammation several years later (Slopen et al., 2014). In prepubescent youth, exposure to violence is associated prospectively with telomere shortening (Shalev et al., 2013), and telomere shortness in early childhood predicts carotid artery thickness several years later, and during puberty (Barraclough et al., 2019; Skilton et al., 2016).

Early adversity may accelerate aging in part through inducing early puberty which in turn is linked to earlier onset of metabolic disease (Gur et al., 2019; Sun et al., 2017). Early adversity may also initiate a trajectory of early aging through lower reserve capacity such as low optimism and higher stressful events in adulthood (Lee et al., 2019; Surachman et al., 2019). Early adversity also predicts poor health behaviors such as sedentariness, smoking and substance use in youth (Wiehn et al., 2018) and these habits appear to persist long into adulthood (Hughes et al., 2017).

3. How to best measure biological aging to predict healthspan

3.1. Cellular aging

The pillars of mammalian aging, represent fundamental and related pathways such as genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, metabolic pathways such as deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, macromolecular damage, chronic low-grade inflammation, and adaptation to stress (Kennedy et al., 2014; López-Otín et al., 2013). Other hallmarks of cellular aging are being identified in the brain (Mattson and Arumugam, 2018). Molecular pathways are often not closely related to each other, pointing to the use of algorithms, for better prediction of outcomes, described below. Several of these basic mechanisms in immune cells have been associated with aspects of social stress, including systemic inflammation and shorter telomeres (Epel et al., 2004; Kiecolt-Glaser et al., 2011; Miller et al., 2008) poor mitochondrial function (Picard et al., 2018), and accelerated epigenetic aging (Park et al., 2019; Wolf et al., 2018). **These associations with lifespan stress demonstrate there is no closed system of intrinsic aging, and even at these molecular levels our aging rate is influenced by our life exposures**. We cannot rule out the possibility that some of these observations are from transgenerational effects.

3.2. Multi-system aging

A new practical approach already used in humans is to measure a panel of biomarkers of aging that reflect cumulative damage across regulatory systems (e.g., metabolic, immune, stress related), and reducing this to a composite measure. The first of these measures was allostatic load (Seeman et al., 2001), and there are newer algorithm measures like 'pace of aging' (Belsky et al., 2017a), and lack of normal covariation among regulatory systems (Belsky et al., 2017b). These measures serve as a barometer of biological aging across the lifespan, linked to early experience, and may be useful to examine the effect of interventions (Moffitt, 2020). So far, the markers used have been chosen out of convenience of availability, but there is exciting potential to develop further translational measures based more directly on the basic mechanisms of aging. This admittedly requires high intensity collaboration between basic and clinical scientists (eg, assessments of mTOR activity, senescent cells, mitochondrial functioning).

3.3. Speed of recovery as a novel measure of latent aging at any age

Geroscience recognizes that physiological adaptation to stress stands out as a common phenotype of aging across model systems of aging. Stress resilience, and its impairment, is partly an outcome of the social hallmarks of aging, and a common underlying process that in part regulates the cellular hallmarks of aging. Snapshot cross-sectional measures of aging based on blood have inherent limitations in that they do not directly test how a person responds to an acute stressor. Recovery from challenge is a critical measure of stress resilience that may be important, as it assesses the latent homeostatic capacity of a system. Speed of recovery is thought of as intrinsic homeostatic capacity, a latent capacity that reflects biological aging. Recovery is such an important marker of aging that it is central to the emerging areas of 'physiological geroscience" and "translational geroscience." Naturalistically, acute events often precede a rapid decline in function, reflecting lack of stress resilience. For example, 50% of new disabilities develop after an acute accident or illness and hospitalization (Gill et al., 2004). There are many examples of paradigms measuring recovery that have validated the importance of using a challenge, and measuring functional or biological recovery from the challenge.

Frailty is a measure of advanced biological age that reflects loss of stress resilience due to age related decline in physiological reserve (Hoogendijk et al., 2019). However, frailty is a final common pathway, one that is probably not reversible. Stress resilience interventions will need to target people earlier in life long before frailty sets in. In contrast physiological resilience, which refers to physiological ability to bounce back from a stressor, is measurable at any age (Whitson et al., 2016, 2018).

4. Stress resilience and reserve capacity

Stress resilience depends in part on the pre-existing level of **reserve capacity,** the positive protective factors of an organism, as well as the immediate adaptive psychological response to stressors (cognitive appraisals). In the stress literature, reserve capacity has been defined as combination of personal resources such as optimism and sense of control, and social factors such as social support. High psychosocial reserve capacity appears to buffer those from low SES backgrounds from developing cardiovascular disease (Matthews et al., 2008). In geroscience, reserve capacity refers to a broader set of resources of or buffers, social, psychological or physiological including cognitive function (e.g., high IQ), physiological (e.g., aerobic fitness, sleep), and psychological assets (e.g., high optimism or positive affect).

High reserve capacity increases the likelihood that one will have a hormetic protective response to a stressor. As shown in Fig. 2, after diverse types of stressors (eg, chemical, physiological or psychological), an organism reacts and recovers to baseline with different speeds and this is moderated by baseline reserve capacity. For example, in response to hip replacement surgery, the biggest predictor of good recovery was reporting good physical function at baseline (Colón-Emeric et al., 2019). In response to general anesthesia, predictors of protection from dementia and other cognitive outcomes included measures of cognitive reserve such as education and vocabulary ability (Cizginer et al., 2017). Indices of reserve capacity in functional abilities (such as ability to stand, gait speed, level of fitness), and glucose-insulin response to a glucose load, predict time to mortality, as reviewed elsewhere (Seals and Melov, 2014).

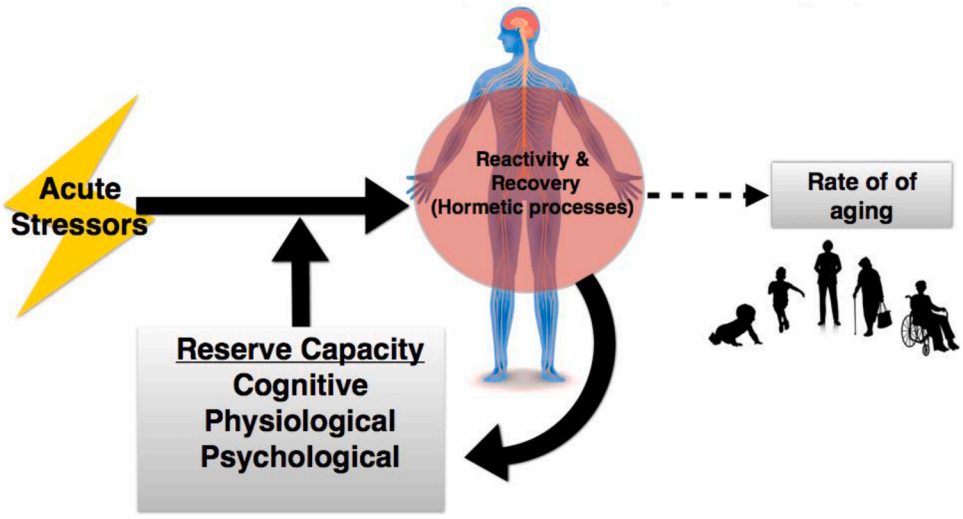

Fig. 2. Individual variance in acute stress response moderated by Reserve Capacity. In response to **acute stressors**, individuals have a kinetic trajectory of responses across psychological and physiological regulatory systems that lead to **reactivity and recovery** profiles. Resilient stress responses (typically rapid high peak and rapid recovery) often have hormetic effects at the cellular or systemic levels. High levels of **reserve capacity** predict more rapid recovery, and this may lead to a positive feedback loop promoting even higher reserve capacity. Level of stress resilience is multiply determined by the social context and individual reserve capacity. Together the latent homeostatic capacity of the organism to have resilient stress responses serves as an indicator of biological age and over time may influence the **rate of aging**.

One of the most well-developed areas of reserve capacity comes from examination of individual dispositions of temperament, typically called personality traits. There are many psychological assets in adulthood that are associated with both better recovery from stressors, and with health and mortality. These include optimism, positive affect, mindfulness, coping with stress with cognitive reappraisal or active coping, high presence of social support or seeking support, purpose in life, and quality relationships. Many of these assets have been associated with indices of good health, such as self-reported health and higher heart rate variability (Carnevali et al., 2018). These positive assets are shaped by genetics and life experience. Heritability and GWAS studies show substantial polygenetic influences, up to 40%, on personality traits such as neuroticism and positive emotionality (Vukasović and Bratko, 2015), traits that shape risk or resilience to depression (Laird et al., 2019; Sanchez-Roige et al., 2018).

It has long been known that poor mental health, one of the social hallmarks of aging, has major effects on recovery from stressors. For example, for heart disease patients, depression increases risk for slower recovery and early mortality (Gathright et al., 2017). High optimism, the most studied positive asset, is linked to fewer cardiac events and lower mortality across studies of heart disease patients, even after controlling for depression (DuBois et al., 2015; Rozanski et al., 2019).

5. Resilience interventions as 'stress inoculation'

5.1. Stress Inoculation

The concept of stress resilience across systems has implications for primary prevention, as well as secondary prevention in the elderly, and possibly rejuvenation. However, there are few interventions precisely targeted toward building stress resilience, that promote speed of recovery from a stressor. Stress inoculation entails exposing people to short term stressors, which leads to a more resilient response upon future exposure.

In the basic research aging literature, '**pre-conditioning**' is similar to the idea of stress innoculation. In these paradigms, prior stressor exposures lead to enhanced protective responses, compared to naïve unexposed controls who are exposed for the first time (Calabrese, 2016).

Table 1
Examples of Interventions for Stress Resilience at the individual and Social levels.

	Stress rejuvenescence	Stress acceleration of aging
Individual biological factors		
Temperature	Intermittent hyperthermia or hypothermia	Static temperature
Breathing	Intermittent hypoxia	Chronic shallow breathing
Exercise	Intermittent high intensity training	Sedentary
Nutrition (types)	Phytochemicals from foods	Traditional American diet
Nutrition (timing/amount)	Intermittent fasting mimicking	Excessive caloric intake
Individual psychological factors		
Psychological stressors (exposure)	Intermittent, manageable	Chronic, or absence
Psychological responses and assets	Challenge mindset, optimism, purpose in life, mastery	Threat mindset, pessimism, lack of purpose, low mastery
Cognitive stimulation	Intermittent challenges	Absence of challenges
Social intervention targets		
Neighborhood programs	Safe cohesive neighborhood	Violence exposure
Pregnancy programs	Support during pregnancy	Toxic stressor exposure
Nutrition programs	Food security	Food insecurity
Group culture trainings	Social support/belongingness	Loneliness, Depression

One emerging example at the physiological level is the use of ischemic preconditioning (cycles of blood pressure cuff constriction) which appears promising for improving blood pressure and cardiovascular related outcomes in older participants, and improving heart rate recovery in athletes (Arriel et al., 2020; Epps et al., 2016; McLeod et al., 2017). This preconditioning effect has been called building "biological shields" and has great potential for therapeutics using this controlled exposure model (Calabrese and Agathokleous, 2019). The hope is that over time, the positive feedback of hormetic responses to acute stress will promote further positive responses to future stressors, and in turn this will slow the rate of aging in humans, as shown in Fig. 1.

5.2. Exposure to intermittent acute stressors

How can we best translate hormetic interventions to humans? There are many potential interventions that may improve stress resilience, listed in Table 1. Lifestyle interventions, such as exercise, caloric restriction, intermittent fasting, challenging cognitive activities, and response to phytochemicals in vegetables and fruits, are thought to work in part through hormesis (Mattson, 2008b; Radak et al., 2017). At least one research group is pilot testing a cocktail of stressors in humans to examine rejuvenation effects, using intermittent cold, heat, fasting and hypoxia, together with phytochemicals (Pruimboom et al., 2016). The hypoxic preconditioning effect demonstrates protection of neurons and cardiac cells, and is a potential area of translation (Li et al., 2017). An interesting novel intervention inducing acute stress (through exposure to intermittent hypoxia and cold, also called the Wim Hof Method) appears to improve immune response to endotoxin at least in a small initial study, with a replication effort underway (Kox et al., 2014). At UCSF we are testing a similar protocol to see if this hormetic protocol improves autonomic and neuroendocrine response profiles (including a quicker recovery from acute stress). Another dramatic way to increase stress resilience is to enter periods of fasting, or fasting mimicking with low calories. In rodents, this leads to stress resistance and regeneration and rejuvenation processes through hormesis, in part by down regulating GH, IGF-1, mTOR, and PKA signaling (Longo, 2019; Rangan et al., 2019).

5.3. Building reserve capacity

Reserve capacity is built during formative developmental experiences, such as level of education, attachment relationships, and manageable stress exposures that shape the neural architecture of stress responding, narratives of optimism, and foster positive challenge mindsets. One can build reserve capacity by increasing physiological buffers (fitness, or antioxidant diets), or psychological stress resilience, through psychological trainings that might decrease chronic stress arousal and shape one's mental filter so they habitually perceive less threat. Interventions that build psychological positive assets like optimism, mastery, and purpose in life need to be further developed and refined.

Mind-body interventions have a strong empirical base for improving self-reported well-being (Creswell, 2017) with mixed effects on basal inflammation (Bower and Irwin, 2016). Mindfulness training may lead to changes in heart rate variability and telomere biology, although the evidence again varies by population and study (Rådmark et al., 2019; Conklin et al., 2019) and appears stronger with clinical samples—those with high stress or early disease. There is emerging evidence that mind-body interventions improve physiological acute stress reactivity, changing stress appraisals and physiology to more of a positive challenge profile with a strong peak and faster recovery (Daubenmier et al., 2019; Lindsay et al., 2018)

Health behaviors regulate healthspan. The social hallmarks of aging shape health behaviors from an early age, which track throughout life. Health behaviors, such as diet, physical activity, sleep, and smoking are shaped by social stress. Chronic stress both biologically drives toxic food choices (sugar, fast food), impairs sleep, and promotes addictions, an indirect pathway in **stress-acceleration of aging.** The converse is also true, positive health behaviors promote **stress-slowing of aging**. Seventh day Adventists who practice lifelong positive health behaviors, and lack the adverse behaviors of substance use, tend to have optimal longevity, living at least four years longer than the average US life expectancy and thus being the only blue zone in the US (Fraser and Shavlik, 2001). Exercise is the prototypical hormetic intervention. It increases the odds of healthy aging by 39% (Daskalopoulou et al., 2017). The mechanisms at the cellular level are becoming well explicated, as it can enhance mitochondrial health, telomere biology, glucose, V02 max, oxidative stress, and NO and upregulate stress resistance pathways, such as autophagy, and heat shock proteins (Musci et al., 2019; Denham et al., 2015; Mooren and Krüger, 2015; Musci et al., 2019; Puterman et al., 2018). It is still important to understand how high intensity interval training, which is a hormetic dosage compared to endurance training, might have different effects on hormetic processes.

6. Social and behavioral factors shape toxic stress and stress resilience

Creating the opportunity for a long healthspan for all (health equity) requires improving economic and social factors. Social factors are intrinsic to aging, our rate of aging depends on our social context and conditions. Material deprivation and poor neighborhood quality confer psychological stress and risk of poor mental and physiological health (Brisson et al., 2020). For example, food insecurity is associated with over two fold risk of clinical anxiety or depression in adults, and confers even higher risk in college students (Arenas et al., 2019; Leung et al., 2020). We now have a better understanding of how social threats lead to toxic stress. The primary motivational forces shaping human behavior are seeking safety and connection with others, and avoiding danger and anxiety. Our mind is constantly seeking cues for safety or danger, even when we are not aware of this, and these social signals are transduced to biological signals, including patterns of autonomic activity and gene expression that are linked to inflammation. It is thought that exposure to or perception of frequent social threats (such as social rejection, discrimination, violence, and lack of safety) creates higher chronic systemic inflammation and sympathetic arousal, even while sleeping, and greater risk of affective disorders (Brosschot et al., 2017; O'Donovan et al., 2013; Slavich, 2020; Slavich et al., 2010). Conversely, social support, and social capital including perceived safety in neighborhoods, may be stress buffering, and are often associated with less inflammation and longer telomeres (Brown et al., 2020; Rentscher et al., 2020; Thames et al., 2019; Geronimus et al., 2015; Park et al., 2015). Social support and social networks can bolster healthspan interventions: Our stress, emotional and physiological, is contagious to close others (Carnevali et al., 2020; Engert et al., 2019), and conversely positive emotion and positive health behaviors are also socially influenced (Christakis and Fowler, 2013; Kim et al., 2015).

The geroscience interventions that may work in mice will not be useful if they cannot be translated well to humans, taking into account our need for support and the significant challenges we have with adherence to exercise and other lifestyle changes. Poor behaviors can override effects of protective pharmaceuticals. A common example of this is that people still develop diabetes while taking metformin due to overeating a western junk food diet. Improving health behaviors can best be prioritized and implemented in the context where basic social needs are met. Creating a supportive built environment and positive social environment are critical to promoting long-term behavior change. The science of behavior change, including the NIH initiative focusing on this (Nielsen et al., 2018), has dramatically raised the sophistication of the research in this area, using the experimental medicine model to identify and manipulate the behavioral and social factors that facilitate adherence to health behaviors. Behavioral iinterventions that work beyond the individual level, that can decrease loneliness and improve

support will be more successful.

The COVID-19 pandemic demonstrates well the role of social factors in resilience to mental health disorders and infection. The pandemic led to dramatic increases in mental health disorders in the US and other countries (Xiong et al., 2020) but this was not equally distributed. Those with low education, income, minority status, loneliness, or low social support have significantly higher rates of mental health disorders from pandemic stress (Arafa et al., 2020; Holingue et al., 2020; Palgi et al., 2020). These vulnerable groups also tend to have higher rates of COVID severity (Adhikari et al., 2020; Webb Hooper et al., 2020). Any policies that improve social equity are also 'stress reducing' health policies that may contribute to healthspan, and can be incorporated into the geroscience agenda.

7. Geroscience relevance to COVID-19 and climate crisis challenges

Geroscience is now more important than ever, both to our aging global demography but also to the health challenges we face going forward. In our new era we have dramatically increasing temperature extremes, wildfires and small particle pollution, and new zoonotic viruses to contend with intermittently. Thus reducing social disparities, improving stress resilience and bolstering immune function have become critical public health goals.

The vulnerability to COVID-complications, while still largely unknown beyond older age and pre-existing diseases, clearly depends on ability of the immune system to respond robustly. The relevance of immune senescence in COVID-lethality has stimulated many hypotheses about geroscience-related prevention and treatment (Barzilai et al., 2020; Salimi and Hamlyn, 2020; Sargiacomo et al., 2020). While vaccination is essential for traditional prevention, it is not a universal solution: The elderly have poorer antibody responses to vaccination, there are many strains of the current virus, and there will be many proliferations of future viral strains novel to the human body, due to climate change. **Therefore, geroscience interventions now have unique universal importance across time.** Pharmacological interventions have been suggested for COVID such as rapalogs, senoytics, Nicotinamide Adenine Dinucleotide NAD+, and metformin for anti-inflammation, telomere stability, or to boost vaccination response (Omran and Almaliki, 2020). Those with diabetes appear to benefit from metformin, which has hormetic properties, to prevent COVID-related mortality (Luo et al., 2020).

Beyond pharmacological treatments, it is likely some of the interventions for boosting stress resilience in Table 1 may enhance resistance to viral infections, from common cold to novel viruses. The malleable lifestyle behaviors like fitness, nutrition, sleep quality, and stress reduction, are important ways to reduce insulin resistance and comorbidities, and thus may help prevent immune senescence and COVID complications.

One pathway through which stress resilience interventions could impact immunity is through stabilizing telomere length. Short telomeres predict greater vulnerability to rhinovirus infection, acute respiratory syndrome disorders, and mortality from sepsis (Cohen et al., 2013; Liu et al., 2020). Chronic psychological stress shortens telomeres in animal studies (Epel and Prather, 2018) and impairs viral immunity (Cohen et al., 1991, 1998). Short telomeres indicate lower ability to mount a robust replicative T cell response, and this may be a critical or even fatal limitation in the face of COVID related lymphopenia (Aviv, 2020). In short, COVID-19 presents a potent example of the potential for using indices of aging as predictors of disease and targets of intervention.

8. Conclusions

The goal of geroscience is to slow aging to improve healthspan. In the next generation of research, we will benefit greatly from incorporating the the important malleable factors that impact human aging—biobehavioral and social factors. The NIA's Intervention and Testing Program, a multi-institutional infrastructure to study biological agents for healthspan in animals is a model that can be extended to human trials that takes into account the social and behavioral factors (Moffitt, 2020, this issue). The social hallmarks of aging shape rate of aging, in part through toxic stress processes. The understanding of toxic stress and hormetic stress as factors shaping aging in opposite ways will have implications for interventions. Stress resilience, the ability to recover quickly and turn on rejuvenative processes, is an important dynamic endophenotype of healthy aging. It remains to be seen how much resilience is merely a characteristic of healthy aging or a causal factor, although much evidence reviewed here suggests it is at least partly causal. A better understanding of how to measure stress resilience, and to promote stress resilience at the cellular, physiological and psychosocial levels will lead to important gains in slowing aging. The science of stress is an integral part of geroscience, and offers insights on how to harness stress for optimal longevity, and implications for how to conduct the most effective interventions incorporating these stress processes as both target mechanisms and outcomes.

By having an integrative paradigm that can be examined across levels, we can reduce the gap between physiological stress research in model organisms and human research on stress, resilience and adaptation. There are many ways to measure biological aging in humans that can serve as a barometer of change for interventions. This includes cellular level markers, multi-system composites, and ways of examining dynamic stress resilience, as reviewed. This can include recovery from a medical event in the elderly, but also recovery to standardized challenges, and to naturalistic psychosocial stressors.

Geroscience offers an exciting opportunity for high impact interventions. This integrative paradigm can shape the next generation of researchers. The training models need to bridge the many fields as outlined by pioneers in geroscience (Newman et al., 2019). Models which are focused on pharmacological interventions must expand to be inclusive of both social and behavioral interventions, the current 'big levers.' Lastly, this field, like all of science, needs to actively encourage and support young investigators from diverse and underprivileged backgrounds to enter this important and growing field which has the potential to minimize socioeconomic and ethnic/racial health disparities. This is not just for equity but also for the improved science that results by including people with diverse life experiences and perspectives.

Frameworks for proof of concept trials related to loss of physiological resilience have been initially outlined (Justice et al., 2016), and there are many geroscience trials in the field. These human trials can draw on the rich insights from decades of biobehavioral basic and intervention research. The Science of Behavior Change initiative at NIH is supporting the development of more effective behavioral and social interventions using the experimental medicine model, and thus applying the same attention and rigor as pharmaceutical studies. By working across disciplines, with an understanding of the role of lifespan experiences, and complexity of human environments, the geroscience framework has tremendous potential for breakthrough innovations in increasing healthspan.

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Appendix A. GEROSCIENCE RESILIENCE GLOSSARY

There has been a proliferation of terms from related disciplines that overlap and are differentiated here. The discipline most often using the term is noted, but these terms could be used to describe all levels of

analysis, including cellular, physiological/organ systems, or psychological, behavioral and social processes. Resilience has also been applied at the systems level, to organizations, communities, societies, and ecosystems.

Adaptation to stress. How systems change in response to stressors, typically referring to level of hormetic responses–protective adaptive responses in cells such as heat shock protein increases.

Hormesis. The adaptive response of cells and organisms to mild/moderate stressors. Mild stressors induce adaptive capacities that protect an organism for a short while from future stressors and may improve the physiological state of that organism. **Preconditioning** is a case of hormesis where exposure to a chemical agent leads to a 30–60% stronger adaptive response to subsequent exposures, across cell types and stressors (Calabrese, 201). In psychology, the term **stress inoculation** is used in a similar way.

Stress Resistance. Showing little or no response to an acute challenge. Higher stress resistance means the cell or organism can tolerate higher levels of stress as the response curve is typically shifted to higher doses of stress. **Multiplex stress resistance** occurs after hormetic exposures, when cells show little response to the initial stressor but also show little response to other types of stressors as well.

Stress Resilience. *The American Psychological Association* definition is limited to a macro level response, "the process of adapting well to adversity, trauma, tragedy, threats or significant sources of stress," Here we take a cross disciplinary approach: The level and speed of recovery of any functional response, including psychological or physiological responses, back to baseline levels after an acute challenge. It is common to use a lab stressor or naturalistic stressor, in, clinical psychology, health psychology, and psychophysiology research.

Physiological resilience. Like stress resilience, this refers to the level and speed of recovery to baseline of a regulatory system or outcome after acute challenge. It often includes clinical outcomes such as recovery from surgery or speed of wound healing in psychoneuroimmunology. A newer term used for this is **homeostatic capacity.**

Frailty: a common condition developed in the elderly characterized by enhanced vulnerability to the effects of a stressor, in that one does not recover quickly or well.

Reserve capacity: An individual's resources in a particular domain (cognitive, physical, psychological, social), which can promote rapid recovery from a stressor. For example, in geroscience, high **physiological reserve** (having a strong physical condition or fitness at baseline), would promote greater physiological resilience to a stressor. In psychological research, high levels of optimism or social support promote faster recovery.

Enhanced allostasis/physiological thriving. In response to a stressor, when one becomes more resilient in their stress responses, with low baseline levels of stress arousal and quick recovery.

Optimal aging. Living both with high functioning and good health (healthspan) and for a longer period (longevity).

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