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COMMENTARY: Foundational social geroscience: Social stress, reproductive health, and lifecourse aging across mammals

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We are at an exciting moment in the science of aging, with an explosion of ways to measure biological aging at the molecular level. These biomarkers may be of limited use without understanding lifecourse and intergenerational aging, and the rich insights from comparative animal studies. The special issue of Neuroscience and BioBehavioral Review "Social dimensions of health and aging: Population studies, preclinical research and comparative research using animal models provides an impressive collection of findings from humans and other mammals. Each article (including the ones I will comment on led by Drs Lyon, Dettmer, Hernandez-Pacheco, Shively and Tung) integrates human and animal studies, and together sheds light on some universalities across many species. These comparisons help us focus on what might be called "Foundational Social Geroscience."

For example, as reviewed within, observational studies in humans and in long lived mammals show the link between early life adversity (maternal loss) and shortened lifespan. Many show a link between early adversity and "reproductive fitness" or number of offspring. Learning about the Social Geroscience of even just one species, studies following apes or chimpanzees over decades, inspires both awe and humility. Comparing across species, as many of these reviews do, reveals the inherent complexity of how social stress and social support shape aging, sometimes species specific, always context dependent. Tung et al. (2023) show that in wild baboons, early adversity, lifetime social connection, and glucocorticoids, while associated with each other, have independent effects on lifespan, and thus early adversity effects on baboon aging involves "multiple weak mediators." This is a lesson mirrored by human data on lifespan as well.

Social Stress is inherently part of biological aging: In a novel integrative review of human and animal research, Lyons et al., (2023), this issue, show the links between chronic stress and hallmarks of aging, such as mitochondrial health, telomere attrition, oxidative stress, inflammation, epigenetics (Figure 1, Lyons et al., (2023). This body of work raises the question to what extent stress should be incorporated into models and interventions for aging. Intrinsic aging can be thought of as the biological process of chronological aging, whereas extrinsic aging can be thought of as external exposures, including stress, that impact rate of intrinsic aging. However, stress is not exclusively extrinsic, given the co-regulation and overlap between many stress and hallmark of aging cellular processes, such as chronic inflammation and mitochondrial energetics (Bobba-Alves et al., 2023). It is always present to varying extents throughout the lifespan. It thus may be useful to think of chronic social stress as a mediator (not just a moderator) of rate of mammalian aging. Natural aging includes an intricately interdependent process of stress-induced rate of aging, making it critical to identify stress pathways for intervention.

In humans, the main "social hallmarks of aging" (mental health, adverse events, low socioeconomic status, and minority status)— are relatively large predictors of morbidity, whereas biomarkers tend to constitute multiple weak mediators or predictors (Crimmins, 2020). These social hallmarks are also sources of high psychological stress, emphasizing the importance of directly measuring relevant stressors and stress responses throughout sensitive periods in the lifespan (See NIH Stress Network Toolbox, www.stressmeasurement.org, for validated measures).

The study of stress-induced aging must incorporate reproductive factors: Stress shapes female reproductive health, and pregnancy health, which in turn affects offspring health and must be further incorporated into human models of aging. Evolutionary models of aging show timing of reproductive lifespan may influence lifespan. As reviewed within, many animal models find early life adversity can reduce reproductive fitness (the number of offspring), or the converse, safe conditions like ample food (vs. food insecurity) can increase reproductive fitness. In humans, it is now established that early life adversity can induce early puberty, which is associated with worse mental and physical health for females. We have for example linked early puberty to an aging phenotype in midlife (Hamlat et al., 2023), and secure maternal attachment and lower adiposity may delay it (Bleil et al., 2021). Earlier menopause predicts earlier cardiovascular disease onset but few human studies have examined stress and timing of menopause. Although sex differences in lifespan are robust, and estrogen is linked to many improved hallmarks

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of aging, there are no well established interventions based on hormones or timing of reproductive events to delay aging.

In this issue, Shively et al. (2023), review how social stress (low status) and poor diet (Western diet vs. Mediterranean diet) affect multisystem aging in macaques. They found independent and additive effects – stress and poor diet increased cortisol and sympathetic reactivity, and create multiple disease risk factors including poor muscle mitochondrial function, visceral adiposity and insulin resistance. Notably social stress impairs ovarian function, and those with poor diets and subordinate status had the lowest progesterone and irregular cycles, which in turn will likely hasten cardiovascular disease development and shorten healthspan. A single biomarker approach (such as tracking epigenetics) to monitor intervention effects will miss the important stress effects on adiposity and reproductive health, critical to understanding prevention of lifecourse aging.

The future of interventions, natural experiments, and climate change. Slowing stress-induced aging may be one of our most malleable and accessible levers to slow aging. This leads us to interventions that can reduce social stress pathways (improving policies, environments, behaviors, relationships). In addition, at an individual level, we can slow aging through promoting restorative pathways. Prolonged deep rest states, such as mind body practices and deep sleep, can reverse stress effects, and may induce reparation and restoration of cellular damage, promoting optimal cellular function to slow aging (Crosswell et al., 2024).

We are living in a time of high existential population stress, often labeled the polycrisis. Dettmer and Chusyd (2023) share that for several species, elephants and hyenas, the effects of ecological early life adversities, such as drought, were greatest when combined with social early life adversities. Climate change disasters and mass migration will accelerate aging trajectories, as we already know that pollution, heat and displacement impact some of the hallmarks of aging such as telomeres, and oxidative stress including during pregnancy and in exposed offspring. In our future, given the increasing number of ecological disasters, and the trauma and anxiety that results from these uncontrollable exposures, on top of a growing mental health epidemic, we can expect increasing stress-induced aging effects that we cannot ignore. These natural "experiments" will affect all species.

Overall, the findings in these reviews, and an emphasis on reproductive transitions as critical periods for stress-induced aging and potential interventions, make the case for Foundational Social Geroscience. This field capitalizes on rigorous methods such as the use of evolutionary biology comparative studies, as well as natural and controlled experiments, to manipulate social stress, to examine sex differences, effects on reproductive timing, healthspan, and intergenerational effects on offspring health. In humans, a lifecourse approach allows us to also examine response to traumatic events including ecological disasters, as well as to periods of major social transition (e.g, divorce, retirement, bereavement) that have the potential to induce prolonged periods of perceived chronic stress, anxiety, or depression. Given that these chronic emotional stress states can have larger and lasting effects on aging biology when they occur during sensitive developmental periods, including fetal development, early childhood, and reproductive changes, stress-induced aging is rarely if ever linear. Chronic cumulative stress may speed overall rate of aging, but acute social adversities and health events create abrupt accelerations that can't be well detected with linear models. Rather, as Hernández-Pacheco et al. (2023), this issue, point out, modeling acute changes with multi-state models may be more fruitful. In sum, forging more parallels and bridges between animal and human longitudinal observational and interventional studies (i.e., reducing stress or increasing prosocial connections) during critical periods, will sharpen our focus on the most promising paths forward toward healthy global aging, particularly during the polycrisis period.

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