Neurobiology of Aging 131 (2023) 222-228

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging.org

Commentaries on A framework for concepts of reserve and resilience in aging

The many faces of resilience

Luigi Ferrucci

National Institute on Aging, NIH

When I was asked to write a piece on resilience, I felt both pleased and fearful. These days the word "resilience" appears in many different contexts, with the most disparate meanings in the science literature and the media. Nevertheless, after few sessions surfing the net, I was ready to start writing. In my mind, I would start with the Webster dictionary definition, glance at the changing concept of resilience in medicine over the years, and then dive into the central role of resilience in the development of Geroscience, the idea that all chronic disease as well as deterioration of physical and cognitive function arise from the biology of aging. Yet, with my fingers already on the keyboard, this all seemed too insufficient and inconsequential for such an important concept. In my heart, resilience is at the core of life, interpreted as the constant battle of entropy and chaos against harmony and beauty.

Transforming my abstract view of resilience into something measurable in science is a challenge. Beyond formal definitions and limiting the discussion to living species, the concept of resilience pertains to the physical and informational resources that allow organisms to survive and thrive despite subjection to stressors. The degree of resilience defines the intensity and duration of stress that an organism can withstand, the amount of unresolved damage that accumulates when stress above a certain threshold is applied, and how fast and how completely the system can reset to a hemostatic equilibrium once the stress dissipates. An elegant example of reliance mechanisms in biology is the "integrated stress response" (ISR), a unique cell mechanism that is sensitive to many types of stress, including amino acid deprivation and accumulation of misfolded proteins. As a resilient system, the ISR responds by shifting available energy to homeostatic signals and if the stress cannot be mitigated, it triggers apoptosis to avoid the spread of damage to the organism. Indeed, in the search for the mechanisms of aging, we have discovered that the so called "hallmarks of aging" reflect the primary resilience mechanisms essential for life and when these fade the stochastic damage that we call aging emerges.

Of course, resilience is not confined to the microcosm of molecules but rather extends its tentacles across all aspects of life. As the list of possible examples would be longer than Don Giovanni's numerous conquests in Mozart's famous opera, I just cite a few: a stroke patient who walks using an alternative motor strategy, a highly educated gentlemen that despite severe brain pathology can still function independently, an older woman with a hip fracture who gets a hip replacement and faithfully adheres to rehabilitation. Moreover, having a positive attitude, being surrounded by loving family and friends, living is a place with clean water, food and adequate medical care and having money are all examples of intrinsic and extrinsic resilience resources that can be summoned to overcome a stressful event and serve as precious companions supporting a successful recovery. In the end, maintaining health and quality of life is all about resiliency in its different forms. And yet, resilience is a dimension almost ignored by modern medicine. When I have my annual check-up, I would like to ask: "Doc. what is my level of resilience?" But I am certain I would receive a skeptical glance and possibly a prescription for a psychiatric evaluation. But I should not be surprised! The medical system is designed to respond to the emergence of pathology rather than improving health by enhancing resilience. It is not by chance that health care users are called "patients". Improving people's health by boosting their resilience would be a transformative shift in the health care system that would necessarily involve many social and environmental aspects of society not currently considered in the domain of health.

Building resilience is not a dream but quite possibly and in part is related to the "hormetic principle" that a little stress stimulates a counteractive response. Exercise is perhaps the best example. In the untrained, a bout of exercise causes diffuse oxidative stress and inflammation followed by a powerful antioxidant and homeostatic response that ultimately exerts beneficial effects on multiple tissues including the brain. There is some evidence that the beneficial effects of the Mediterranean diet on multiple health-related outcomes works in the same fashion. Research on drugs aimed at reinforcing resilience mechanisms is ongoing and in some instances the molecules implicated, named with the neologism "Gerotherapeutics", are being tested in human studies.

Because of the many faces of the word resilience and to avoid confusion, several branches of science are attempting to develop operational definitions that can be expressed as analytic variables in designing experiments and interpreting results. From this perspective, the attempt to confine the meaning of resilience in

neurobiology into precise boundaries should be welcome by the field, especially if followed by expansion of research on the importance of resilience in the development of pathology and its consequences for human life. New ways to enhance resilience at the biological, phenotypic, functional, behavioral, and societal levels are much needed, especially in the face of population aging occurring in the whole world. To accomplish this goal, it is very important to recognize that an agreed upon definition of resilience that can serve as a "Rosetta stone" across different studies but also across research fields is essential to assure we are talking about the same thing and can therefore pool robustness across studies. Having said this, my hope is that the discussion of the universal meaning of resilience will continue. A vivacious universe of symbols beat beneath the surface of this word, and new ideas are waiting for discovery.

To close, I asked ChatGPT to give me a poem about resilience. Below is what I got. apparently, AI can do better than me!

Resilience is the key to life,

A force that cuts through pain and strife,

It's what makes heroes out of men,

And helps them rise again and again.

So, when life's challenges come your way,

And everything seems in disarray,

Remember, it's resilience that will see you through,

And help you find the strength to start anew.

DOI: https://doi.org/10.1016/j.neurobiolaging.2023.07.014

Toward a cosmopolitan appreciation of "resilience" in the world of aging research

Heather Whitson [a], Peter Abadir [b]

[a] *Duke University School of Medicine;*
[b] *Johns Hopkins University School of Medicine*

In October 2022, the National Institute on Aging (NIA) and the American Geriatrics Society (AGS) co-hosted the first of three conferences in a series on "Resilience in Aging Research."

Resilience is a complex and multidimensional concept that has been widely studied in gerontology research, with several parallel efforts in recent years to intentionally develop frameworks and definitions for resilience in older adults (Cesari et al., 2022; Gijzel et al., 2019; Hadley et al., 2017; Ong et al., 2009; Stern et al., 2023; Stern et al., 2019; Whitson et al., 2016). Despite growing interest in resilience, researchers from different domains of aging research have different views on what constitutes resilience. Several factors contribute to this lack of consensus, including disciplinary silos across physical, cognitive, and psychosocial domains; the complexity of the concept; multiple types of measurement tools; and the lack of uniformity in frameworks and outcomes that define resilience. For example, an important component of resilience in many areas of geriatric and psychological research is that a decline in well-being after a stressor or challenge is followed by a dynamic process of recovery or "bouncing back." In contrast, the notion of "bouncing back" from a stressor is not prominent in most brain/cognitive research, where resilience research focuses on factors that help one avoid, delay, or slow a decline in cognitive function.

It is helpful for rapidly advancing areas of science to develop operationalized definitions, and we applaud all efforts to promote synergy and definitional clarity. However, our objective in organizing the NIA/AGS conference series is to mitigate what we see as an unfolding risk. An unintended (and ironic) consequence of parallel efforts to establish consensus terminology is an exacerbation of the Jingle-Jangle Fallacy (Kelley, 1927), if what results is a crystallized set of definitions and shared understanding of "resilience" within silos of aging research that do not align well with each other. The result is a situation where the same term (resilience) is "clearly defined" to mean different things to different groups (Jingle), or a construct that is called resilience by one group is labeled with another term – e.g., reserve, robustness, resistance – by other groups (Jangle).

The NIA/AGS conference in October 2022 was titled "Overview of the Resilience World – State of the Science." The objective was to bring together thought leaders and rising stars representing various domains of aging-related research that have developed important frameworks of resilience. The goal was not to reach consensus on a single unifying framework or comprehensive set of definitions (it is probably too late for that!). Rather, the goal was to encourage dialogue and awareness across fields, to compare and contrast the various resilience frameworks, to consider what could be "borrowed" across them, and to identify any opportunities to elaborate unified working definition(s). More information about the multi-disciplinary conference can be found on this website, and summary documents will be added when they are finalized (https://www.americangeriatrics.org/overview-resilience-world-state-science-2022). In addition, a white paper summarizing this meeting has been published (Abadir et al. 2023) Drs. Yaakov Stern and Carol Barnes, co-authors of the recent consensus framework outlining concepts related to cognitive resilience (Stern et al., 2023), and other brain researchers were important contributors to the conference.

As the multi-disciplinary NIA/AGS conference series continues (with future conferences focused on resilience mechanisms and interventions), it is important that scientific progress and communications about "resilience" should continue to occur within individual disciplines. Thanks to the efforts summarized in the important paper by Stern et al. (Stern et al., 2023), when the term "resilience" is used amongst brain researchers and neuroscientists in the future, it will be better understood as it has been operationally defined there, as a term that encompasses the constructs of cognitive reserve, brain maintenance, and brain reserve. An analogy comes to mind regarding common terms that have different meanings in different countries around the globe: when individuals born and raised in the United States discuss sports, the single word "football" is readily understood to refer to a game that involves helmets and tackling. However, if a cosmopolitan group were discussing sports, it would be important to specify "American football" in order to convey the same meaning to all. Likewise, when communicating with resilience researchers from multiple disciplines, we must be prepared that others may be more familiar with a slightly different framework for "resilience." The addition of specifying terms - e.g., cognitive, brain, psychological, biological, physical, or community resilience – and carefully denoting our framework of reference will help avoid confusion.