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.

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

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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.

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Adapting the reserve and resilience framework for motor and other aging phenotypes

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The conceptual framework presented by Stern and colleagues (Stern et al., 2022) defines *resilience* as the ability to maintain cognition and day-to-day functions despite aging and disease. Operational definitions and guidelines for studying three resilience mechanisms – *cognitive reserve, brain maintenance, and brain reserve* – are then presented to promote a better understanding of factors associated with successful cognitive aging. In this commentary, we discuss evidence for extending this framework to account for unexplained heterogeneous age-related differences observed in other phenotypes like *motor function*. We also review initial attempts to advance mechanistic studies of cognitive and motor resilience.

1. A reserve and resilience framework of motor function can inform cognition
   A reserve and resilience framework that incorporates motor function makes sense because cognitive and motor functions are strongly associated and share neural substrates in aging and dementia (Buchman et al., 2014; Clouston et al., 2013; Cohen et al., 2016; Leisman et al., 2016; Scherder et al., 2007). Gait decline, for example, is an early and reliable predictor of cognitive decline and dementia (Beauchet et al., 2016; Buracchio et al., 2010; Jayakody et al., 2021; Quan et al., 2017). Gait like cognition is also associated with various age-related changes and pathologies in brain regions particularly affected by aging, Alzheimer's disease and related dementia (ADRD) – including (but not limited to) the prefrontal cortex and hippocampus (Allali et al., 2015; Blumen et al., 2018; Buchman et al., 2019; Callisaya et al., 2013; Ezzati et al., 2015; Oveisgharan et al., 2023b; Rosso et al., 2017). Yet, while motor function is a volitional behavior regulated by the brain, cognition and motor function in aging are typically studied in isolation. Adopting reserve and resilience terminology could facilitate a better understanding of cognitive and motor aging and promote the identification of shared and distinct mechanisms of successful aging.
   Analogous to the concept of cognitive reserve, *motor reserve* could be defined as a property of the brain that allows for better-than-expected motor performance despite aging or disease. Likewise, brain maintenance could be defined as the relative absence of brain changes or disease as a cause for preserved motor function in aging. Factors that modify the relationship between brain changes and motor function could then be interpreted in terms of motor reserve and brain maintenance. Direct comparisons of how molecular mechanisms influence the relationship between brain changes and changes in <u>both</u> motor and cognitive functions will be particularly useful for identifying shared and distinct mechanisms. One initial step to facilitate this approach would be to include testing of common motor performances such as gait speed in studies of cognitive resilience. Gait speed can be assessed in most clinical and research settings without specialized equipment and personnel (e.g., timing participants walking a fixed distance down a hallway). Additional aspects of gait and other motor function can be assessed with low-cost, wearable, and unobtrusive sensors that can be employed to obtain remote multiday phenotyping of diverse behaviors during everyday living (Brand et al., 2022; Buchman et al., 2020).
2. Expanding the reserve and resilience framework beyond the brain and cognition
   The reserve and resilience framework developed by Stern and colleagues focuses exclusively on cognition and the brain. Resilience is a general feature of all physiologic systems. The exclusive focus on the brain can lead investigators to ignore other physiological systems that are critical for motor and cognitive function, including musculoskeletal, cardiopulmonary, and metabolic systems (Ferrucci et al., 2000; Rosso et al., 2013). While many essential cognitive resilience networks likely reside in the brain, the neural underpinning of motor control begins in the brain and extends through the entire central nervous system to reach musculoskeletal elements in the periphery that effect all movement (Rothwell, 2012). Accumulating evidence suggest that ADRD pathologies affect not only cognition but also non-cognitive phenotypes like motor function (Albers et al., 2015). While ADRD pathologies extend beyond the brain and accumulate in varied brainstem and spinal cord tissues, resilience mechanisms in tissues outside the brain are understudied (Buchman et al., 2018; Dugger et al., 2013; Oveisgharan et al., 2023a). Identifying tissue-specific and cross-tissue resilience mechanisms within and outside the brain of diverse phenotypes can lead to personalized resilience interventions.
3. Elucidating the molecular mechanisms of reserve and resilience
   The proposed framework focuses on several potential mechanisms that benefit some individuals to age successfully (i.e, manifest slower cognitive decline), but molecular resilience mechanisms like genes and proteins remain relatively unexplored. To fill this