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Comments on framework: The need to include socio-economic status.

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The Framework of Stern et al (2023) discussed the need for longitudinal studies of cognitive maintenance in terms of 'reserve and resilience'. Two recent longitudinal cohort studies document major disconnects between neurodegeneration and cognitive status, the Rush Memory and Aging Project (Boyle et al., 2021) and the National Alzheimer's Coordinating Center (Robinson et al., 2021). From analysis of multiple co-pathologies, both concluded that clinical AD is poorly predicted by only plaques and tangles. Less than one-third of variance in terminal cognitive decline was attributable to eleven pathological indices combined (Boyle et al., 2021). What is missing?

The longitudinal studies of Boyle et al. (2021) and Robinson et al. (2021) did not include SES. I suggest that the gap between pathology and cognitive status in these studies points to domains of 'reserve and resilience' which may vary by SES in parallel with the 10-15 year SES difference in age-risk for dementia (Arapakis et al., 2021; Beydoun et al., 2022; Korhonen et al., 2022) and lifespan (Crimmins et al., 2009). Is the cognitive reserve also smaller for lower SES commensurate with the decade earlier dementia risk?

I suggest that neural stem cells (NSC) might be assayed postmortem as a measure of cognitive reserve. As shown by many studies, the endogenous NSC in adult rodents continue to add new neurons to the hippocampus. Postmortem immunohistochemistry shows endogenous NSC progressively decrease in numbers during aging and AD (Gage 2019; Zhou et al., 2023). NSC merit consideration for contributions to cognitive reserve in relation to SES status.

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A way to the future

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The ability of a brain to function and to exhibit the properties of resilience, reserve and maintenance derive from the properties of individual neurons and its synapses, operating in an ensemble of neurons, their synapses, and other cells. And, these properties are determined by the changing gene expression profiles of individual neurons as they operate in an ensemble. Such gene expression profiles are the basic mechanism for phenomena including impaired stress response signaling, Ca2+ dyshomeostasis and/or dysregulation, mitochondrial function, impaired waste disposal, inflammation, and epigenetics mentioned in the report of Stern et al. Although these aspects are not fully developed in the report by Stern et al, their paper serves a valuable function by defining an operational framework within which to design and interpret cellular/molecular studies of gene expression profiles that are the foundation of resilience, reserve and maintenance. The discussion of imaging and anatomical studies provides further utility by defining for the molecular/cellular biologist optimal regions for investigation.

In designing strategies to understand the underlying mechanism(s) of resilience, reserve and maintenance we must not be seduced by the light under the lamp post, the usually seen, by the fact that they are seen under the microscope and in imaging studies. Although amyloid plaques and neurofibrillary tangles have become conventional markers, we know that the correlation between amyloid plaques and cognitive status in AD is very poor and that the damage is done by soluble precursors of amyloid plaques, which are less often seen. Similarly, phosphorylated/acetylated tau is the entity that deserves attention. By the time neurofibrillary tangles have become visible, most of the damage has already taken place. It is these less often seen phenomena that deserve attention, rather than the plaques and tangles that were described more than a century ago.

The framework presented here represents a valuable start. This reviewer would like to see a next iteration with more specifics that also included integration with cell and molecular biology. In terms of more specifics, it would, for example, be useful to include information about what pertinent information about brain regions is already known and not known from imaging studies. What do we already know about resilience, reserve and maintenance that can be applied to the design of cell/molecular biological studies of these phenomena. What would be some useful ways for all these approaches to come together to lead to an integrated model that provides a comprehensive understanding of resilience, reserve and maintenance from the behavioral level through imaging studies all the way to the level of the physiological and cellular/molecular properties of single cells?

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Authors' response

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The commenters responses to the Framework juxtapose the "edges" of the resilience concept, helping us to better put into context our definitions of cognitive reserve, brain maintenance and brain reserve. On the one hand the universe of "resilience is huge" and the it is clear that the Framework focuses on one specific aspect of resilience. On the other hand, our operational definitions are broad and general, so we recognize the goal should now be to proceed to specify more clearly and specifically what brain structures, molecular pathways, and circuit interactions underlie the cognitive phenotypes that we would call resilient. Similarly, we recognize that it will be important to better specify the influence of social determinants and biological sex. Thus, on the one hand we recognize that the resilience discussed in the Framework is only one of many types of resilience, and on the other hand there is much work to be done in exploring the biological/brain functions, as well as the multitude of environmental, genetic and social determinants, underlying this the specific area of resilience.

Dr Ferucci's comments illustrate how geroscientists and geriatricians view resilience from a "whole person' perspective (even if they also define molecular pathways). It will be important to connect the brain with the whole body in a more global perspective on resilience.

Drs Whitson and Abadir accurately point out that the concept of resilience is extremely broad, and that that the Framework addresses but one aspect of resilience. They provide concrete examples of how hard it is to talk about and to agree on definitions from the most reductionistic to the most holistic point of view. We agree that no one document or framework can establish consensus or a unifying framework or set of definitions. However we believe that our Framework does make a useful attempt at defining several of these terms. Arriving at similar operational definitions for more terms that are in use would be extremely helpful in gaining a consensus on what "resilience encompasses'.

To that end, we thank Drs Blumen and Buchman for providing another cogent example of how the concepts of reserve and resilience could apply to motor function. Again this suggestion expands the concept of resilience beyond the brain to other physiological systems that are critical for motor and cognitive function. We also appreciate their examples of potential molecular resilience mechanisms like genes and proteins.

Dr Rajah provides an excellent summary of how the concepts addressed by the Framework have evolved over time. She emphasizes the need for longitudinal studies, and we strongly agree. Dr. Rajah also stresses that studies examine the impact of social determinants of health, biological sex, and gender life experiences, and how they interact with the concepts discussed in the Framework. Again consideration of these variables is crucial for developing a more representative understanding of neurocognitive aging. Similarly, Dr. Finch stresses the importance of considering status, and racial and cultural differences.

Dr Coleman accurately points out where research into concepts of resilience that we define needs to go from a neuroscience perspective. Our goal now should be to proceed to specify more clearly what brain structures, what molecular pathways, what circuit interactions underly the cognitive phenotypes that we would call resilient (whether it be through mechanisms of brain or cognitive reserve, or brain maintenance).

We therefore thank the commenters for both helping us place the Framework within a broader context, and pointing the way towards the effective utilization of the Framework. The latter will require creative studies on both the human and non-human level. Our hope is that the Framework provides a useful guide for this research, and assists in this process by supplying a common language for investigators to share their ideas and findings.

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