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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