Commentary on "A framework for concepts of reserve and resilience in aging"

M. Natasha Rajah

Toronto Metropolitan University, Canada; McGill University, Canada

The cognitive neuroscience of aging field is generally focused on investigating the neurobiological basis of age-related differences (cross-sectional studies) and changes (longitudinal studies) in cognitive function (Grady, 2012). Declines in the ability to remember past experiences in rich detail (episodic memory) and declines in planning, strategic processing, and inhibition (cognitive control) are hallmarks of normative aging (Craik and Salthouse, 2000). Moreover, when these cognitive processes are affected to a degree that impinges upon one's activities of daily living, quality of life, and independence, they are considered pathological and reflective of dementia (Rajah et al., 2009). In contrast, when an older adult maintains a youthful level of cognitive function and/or performs significantly above age-adjusted normative levels of cognition, they are deemed 'superagers'(Gefen et al., 2014; Karpouzian-Rogers et al., 2023; Rogalski et al., 2013). Neuroimaging techniques (i.e., fMRI) are often used in the field to explore how macroscale differences in brain activity and connectivity relate to individual and group mean differences in cognitive ability with age. Age-related decreases in brain activity and connectivity reported in studies are often interpreted as reflecting functional decline/deficit (Rajah and D'Esposito, 2005). However, this may not be the case if we consider that older adults may simply approach cognitive tasks differently than their younger cohorts or their younger selves (in the case of longitudinal studies), e.g., prioritize different information based on life experience compared to younger adults. The interpretation of age-related increases in brain activity and connectivity is even more challenging (Maillet and Rajah, 2014)!

One thing that the cognitive neuroscience of aging field has highlighted over the past decades is that there is *significant variability* in how age affects neurocognitive function across individuals (Nyberg et al., 2012). The question now is - what factors contribute to this variability? Does the observed variability reflect differences in neurocognitive baseline, or brain reserve and the ability to maintain one's brain reserve? Differences in neurocognitive resilience to the effects of time, and associated exposures to biological, environmental, and societal stressors? Differences in privileged experiences (i.e., high socioeconomic status and other social determinants of health) that support the building of cognitive reserve over time, and may provide individuals with neurocognitive strategies (e.g., increased neural plasticity and cognitive flexibility, alternative routes of processing i.e., functional compensation) to buffer against the effects of age/time (and associated exposures to stressors)?

Determining what differentiates 'super', 'normative' or 'asymptomatic', and 'pathological' cognitive aging from a neurobiological perspective, and understanding what environmental, societal, and biological factors contribute to individual differences in neurocognitive aging is *the* primary task/goal of the cognitive neuroscience of aging and dementia research. Tackling this big goal requires clearer operational definitions of some key concepts that are often used in the field, i.e., resilience, maintenance, cognitive and brain reserve, and compensation. The article "A framework for concepts of reserve and resilience in aging" by Stern, Albert, Barnes, Cabeza, Pascual-Leone, and Rapp does exactly this, and builds on prior work by Cabeza et al(Cabeza et al., 2018), Stern et al (Stern et al., 2018) and others (Arenaza-Urquijo et al., 2019; Arenaza-Urquijo and Vemuri, 2018; Holz et al., 2020). A key proposal in this paper – *that the concept of resilience is overarching, and subsumes the concepts of cognitive reserve, brain maintenance and brain reserve* – helps organize the relationship between these concepts significantly. Furthermore, the clarification of the differences between cognitive and brain reserve is helpful, as often these terms have been used in the field interchangeable, which led to us previously supporting the position that one term 'reserve'(Cabeza et al., 2018). The clarification put forth here, that brain reserve *"does not involve active adaptation of functional cognitive processes in the presence of injury or disease as does cognitive reserve"* is helpful and relates brain reserve to the concept of baseline differences (intercepts). The proposal that longitudinal studies are needed in the field to further clarify concepts i.e., cognitive reserve and brain maintenance is important. One hopes that funding agencies hear this, and will support more longitudinal studies moving forward! Yet, future work comparing measurement of these concepts, and results, between cross-sectional and longitudinal studies is needed given current funding limitations to further advance our understanding of neurocognitive aging.

In reading this paper, I am also struck by the clear need for future studies that examine how social determinants of health (i.e., poverty, education, socioeconomic status), biological sex, and gendered life experiences, interact with these key concepts. Such research is necessary to refine and evaluate the utility of these concepts and move the field towards a more inclusive understanding of neurocognitive aging. Indeed, in a meta-analysis we reported that higher education was found to be more cognitively beneficial for older females than males (Subramaniapillai et al., 2021). However, this may reflect a cohort effect given the lower likelihood of females having the opportunity to pursue higher education in prior generations. Also, it remains unclear how social determinants of health and privilege interact with these concepts. It is possible that a more socioeconomically privileged life may not equate to higher cognitive reserve if cognitive reserve is defined as an active cumulative process. Instead, greater privilege may equal having fewer exposures to biological, environmental, and societal stressors and less demand on brain maintenance-related mechanisms. Increasing the diversity of research participants and directly exploring how sex, gender and social determinants of health interact with the key concepts outlined in the paper by Stern et al (2023) is necessary for developing more representative understanding of neurocognitive aging.

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

Caleb Finch

University of Sothern California

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

Paul D. Coleman

Arizona State University

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.