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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.