

Special Section: Are the rates of age- and amyloid β -associated cortical atrophy influenced by sustained exceptional cognitive functioning in older adults?

Don't forget—Age is a relevant variable in defining SuperAgers

The term “SuperAging” was originally operationalized at Northwestern more than 10 years ago based on three criteria: (1) age (80+ years); (2) episodic memory performance that is at least at the level of cognitively average individuals in their 50s and 60s based on published normative data; and (3) performance in nonmemory cognitive domains that is at least average for age. These criteria were developed and validated through a series of research studies that identified novel anatomical, biological, psychosocial, and genetic features associated with the SuperAging phenotype [1–10]. The knowledge gained from these studies stands to inform strategies for promoting preservation of episodic memory in advanced old age and have relevance for addressing themes of resilience, reserve, resistance, and compensation.

The study by Dang et al. (2019) utilizes the rich data from the Australian Imaging, Biomarkers and Lifestyle study [11] to explore whether “SuperAgers” are protected from amyloid β ($A\beta$)-associated neurodegeneration relative to a cohort of cognitively normal cohort of older adults. However, the minimum age requirement was set at 60 rather than 80 years, which questions whether the cohort of Dang et al. is sufficiently old enough to make meaningful statements about resilience and resistance.

The concept of superior cognition as an index of resilience and resistance becomes more meaningful with age as the magnitude of average decline in episodic memory performance over a time is disproportionately influenced by age. This is evident in Fig. 1, which shows normative values for the delayed recall score of the Rey Auditory Verbal Learning Test [12] by decade. Notably, there is an expected two-point decline on the delayed memory portion of Rey Auditory Verbal Learning Test from age 40 to 60 years and a four-point decline from age 60 to 80 years. Because age is a critical factor when determining cognitive expectations, manifestations of genetic risk, and cumulative exposures to biological wear-and-tear throughout the life span, it is difficult to contextualize the results of Dang et al. with existing Northwestern SuperAging literature as the cohorts do not have comparable inclusion criteria.

Using $A\beta$ PET imaging, Dang et al. found that individuals with superior memory performance at baseline do not necessarily resist $A\beta$ accumulation or age-associated brain vol-

ume loss measured longitudinally. Although the Australian Imaging, Biomarkers and Lifestyle study data are undeniably robust, the results are somewhat unsurprising as elevated amyloid levels have been associated with subsequent risk for neurodegeneration and cognitive decline.

What remains unknown is why some individuals in advanced old age are able to maintain superior cognition despite the presence of significant amyloid and/or other seemingly deleterious neuropathologic burden. This latter question is central to the theme of resilience and could potentially be addressed with data from individuals over age 80 in the Australian Imaging, Biomarkers and Lifestyle study cohort given the robust sample size and availability of longitudinal data and imaging biomarkers.

The renewed enthusiasm in identifying factors contributing to optimal aging trajectories is evident in the recent

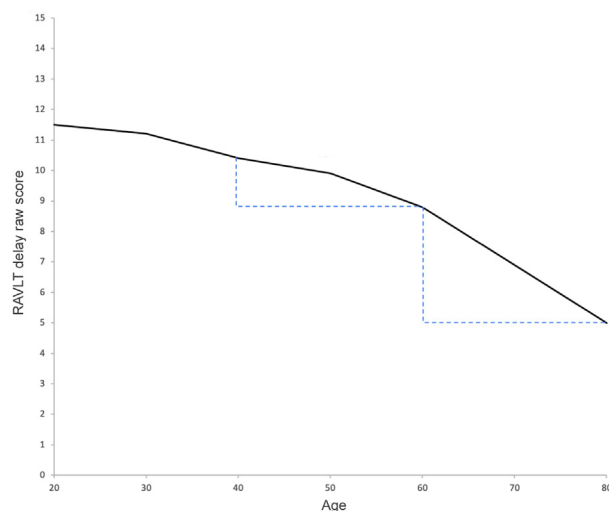


Fig. 1. Nonlinear decline in average episodic memory performance with age. Average episodic memory performance on the delayed recall portion of the RAVLT is provided by decade from age 20 to 80 using normative data. Dotted lines highlight differential magnitudes of decline over two 20-year periods showing steeper performance drops from age 60 to 80 than age 40 to 60. Thus, individuals over age 60 are at risk for more precipitous decline than those who are younger. Chronologic age is a critical variable when defining “youthful” memory performance. RAVLT, Rey Auditory Verbal Learning Test.

Cognitive Aging Summit III, funding initiatives, and “approved concepts” led by National Institute on Aging and the National Advisory Council on Aging. Studies focused on better than expected memory performance in advanced age provide a clever lens to disentangle themes of reserve, resilience, resistance, and compensation and may also offer opportunities to clarify complicated relationships between aging and accumulation of Alzheimer’s neuropathology.

Emily Joy Rogalski^{a,b,*}

^aMesulam Center for Cognitive Neurology and Alzheimer’s Disease, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

^bDepartment of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

*Corresponding author. Tel.: +312-503-1155; Fax: +312-908-8789.

E-mail addresses: erogalski@gmail.com; e-rogalski@northwestern.edu

References

- [1] Cook AH, Sridhar J, Ohm D, Rademaker A, Mesulam MM, Weintraub S, et al. Rates of cortical atrophy in adults 80 years and older with superior vs average episodic memory. *JAMA* 2017;317:1373–5.
- [2] Cook Maher A, Kielb S, Loyer E, Connelley M, Rademaker A, Mesulam MM, et al. Psychological well-being in elderly adults with extraordinary episodic memory. *PLoS One* 2017; 12:e0186413.
- [3] Gefen T, Papastefan ST, Rezvanian A, Bigio EH, Weintraub S, Rogalski E, et al. Von Economo neurons of the anterior cingulate across the lifespan and in Alzheimer’s disease. *Cortex* 2018;99:69–77.
- [4] Gefen T, Peterson M, Papastefan ST, Martersteck A, Whitney K, Rademaker A, et al. Morphometric and histologic substrates of cingulate integrity in elders with exceptional memory capacity. *J Neurosci* 2015;35:1781–91.
- [5] Gefen T, Shaw E, Whitney K, Martersteck A, Stratton J, Rademaker A, et al. Longitudinal neuropsychological performance of cognitive SuperAgers. *J Am Geriatr Soc* 2014;62:1598–600.
- [6] Harrison TM, Weintraub S, Mesulam MM, Rogalski E. Superior memory and higher cortical volumes in unusually successful cognitive aging. *J Int Neuropsychol Soc* 2012;18:1081–5.
- [7] Huentelman MJ, Piras IS, Siniard AL, De Both MD, Richholt RF, Balak CD, et al. Associations of MAP2K3 gene variants with superior memory in SuperAgers. *Front Aging Neurosci* 2018; 10:155.
- [8] Janeczek M, Gefen T, Samimi M, Kim G, Weintraub S, Bigio E, et al. Variations in acetylcholinesterase activity within human cortical pyramidal neurons across age and cognitive trajectories. *Cereb Cortex* 2018;28:1329–37.
- [9] Rogalski E, Gefen T, Mao Q, Connelly M, Weintraub S, Geula C, et al. Cognitive trajectories and spectrum of neuropathology in SuperAgers: The first 10 cases. *Hippocampus* 2019;29:458–67.
- [10] Rogalski EJ, Gefen T, Shi J, Samimi M, Bigio E, Weintraub S, et al. Youthful memory capacity in old brains: anatomic and genetic clues from the Northwestern SuperAging Project. *J Cogn Neurosci* 2013; 25:29–36.
- [11] Ellis KA, Bush AI, Darby D, De Fazio D, Foster J, Hudson P, et al. The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging: methodology and baseline characteristics of 1112 individuals recruited for a longitudinal study of Alzheimer’s disease. *Int Psychogeriatrics* 2009;21:672–87.
- [12] Schmidt M. *Rey Auditory Verbal Learning Test: A Handbook*. Western Psychological Services; 2004.