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Are superagers super rare?

Yuta Katsumi, Ph.D.[1]*, and Alexandra Touroutoglou, Ph.D.[1,2,3]

[1]Frontotemporal Disorders Unit, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA
[2]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA 02129, USA
[3]Alzheimer's Disease Research Center, Massachusetts General Hospital, Charlestown, MA 02129, USA

***Corresponding author:** Yuta Katsumi, PhD, Rm 10.028, 149 13th St, Charlestown MA 02129, USA, Email: ykatsumi@mgh.harvard.edu, Phone: +1 617-726-6201

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Commentary on **PREVALENCE OF COGNITIVE 'SUPER-AGEING' IN THREE AUSTRALIAN SAMPLES USING DIFFERENT DIAGNOSTIC CRITERIA" by Powell et al**

Cognitive abilities typically decline as people age, yet there is substantial individual variation. Previous research on remarkable older adults sometimes called “superagers” has demonstrated that age-related cognitive decline is not inevitable and that some individuals exhibit memory function that is comparable to younger adults. The term superaging was coined by Mesulam, Rogalski, and colleagues, who defined superagers as individuals over 80 years old whose delayed recall score of the Rey Auditory Verbal Learning Test was at least as good as normative values for 50-65 year olds (Harrison et al., 2012). Based on a similar measure of memory function (the long delay free recall score of the California Verbal Learning Test [CVLT]), our group was the first to identify superagers in a younger cohort of older individuals (60-80 years old). These superagers exhibited memory performance comparable to 18-32 year olds (Sun et al., 2016).

Subsequent studies of superaging have employed differing age ranges, neuropsychological tests, and in some cases, longitudinal repeated measures. This has resulted in a number of criteria for classifying an older adult as a superager. In addition to the minimum age of superagers (e.g., 60 or above vs. 80 or above), studies also vary in the age of the reference group; for example, some studies of superagers over 60 years old have compared their performance on the CVLT with 18-32 year olds (Katsumi et al., 2021; Sun et al., 2016; Zhang et al., 2019), whereas others compared performance with 30-44 year olds (Dang et al., 2019). While superagers are most defined by a combination of measures of episodic memory and executive function, some studies have begun utilizing measures of global cognition as well as performance in other cognitive domains (Maccora et al., 2021; Pezzoli et al., 2023). Finally, some studies have defined superagers longitudinally by requiring them to maintain youthful performance in memory and other cognitive domains over 12 years (Maccora et al., 2021). Despite the considerable heterogeneity in these definitions of superagers, no studies to date have compared them within the same sample to examine how these differences might lead to differing estimates of the prevalence of superagers.

The results presented by Powell et al. (2023) published in *International Psychogeriatrics* are significant because they demonstrate how the frequency of superagers in a given sample is affected by the precise demographic and neuropsychological criteria used to define them. In this study, different superaging criteria were variably associated with functional impairment, neuroimaging features, and dementia incidence. Specifically, in examining three independent

cohorts of older adults using nine different definitions[1] of superagers, the authors found that the prevalence of superagers varied from 2.9%, by the most stringent criteria, to as high as 43.7%. This finding suggests that, although superagers have sometimes been conceptualized as a rare subgroup of older adults (e.g., Maher et al., 2022), exactly how rare they are might depend on the specific definition. Not surprisingly, agreement between superaging definitions was also variable; higher agreement was observed when those with similar neuropsychological criteria were compared. It is noteworthy that the highest agreement (κ = .83) was found between the definitions of superagers above the age of 60 that varied in the age of the reference group (i.e., 18-32 vs. 30-44 year olds). This finding suggests that the frequency of superagers in a given sample is not affected fundamentally by the age of younger adults with whom superagers are compared.

In addition to prevalence estimates, the Powell et al. study adds to the literature of resilience to Alzheimer's disease (AD) in superaging by showing that superagers have lower incidence of dementia. This finding is in line with another study published in *International Psychogeriatrics* in which the authors found that older adults who had maintained episodic memory function over 10-15 years showed a decreased risk of developing dementia compared with those who had exhibited memory decline (Josefsson et al., 2023). The low incidence of dementia found in superagers is consistent with prior evidence demonstrating that while superagers and their peers did not differ in polygenic risk for AD (Spencer et al., 2022) or levels of amyloid plaques in their brains (Borelli et al., 2021; Harrison et al., 2018), they nonetheless showed no memory decline, suggesting that they may be resilient to negative effects of the disease on cognition. Superagers seem to also have reduced tau pathology accumulation compared with their peers (Nassif et al., 2022; Pezzoli et al., 2023), suggesting that their brains may also be more resistant to this aspect of AD-related neuropathologic changes. These findings have important implications for research on preventing cognitive impairment associated with AD.

While the study by Powell et al. (2023) makes a novel contribution to the literature on superaging, it is important to acknowledge its limitations. Powell et al. found that superagers and

[1]It is important to acknowledge that four of these definitions came from studies that did not explicitly use the term "superagers". These studies identified older individuals with superior cognition relative to their own age group and not to younger adults. For simplicity, we consider in this commentary all nine definitions as variants of superaging.

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non-superager participants did not consistently differ in regional brain volumes across definitions, although increased size in specific brain regions including the mid-cingulate cortex (MCC, also called caudal anterior cingulate cortex [ACC]) and hippocampus have been commonly reported in neuroimaging studies of superaging (Borelli et al., 2018; Harrison et al., 2018; Katsumi et al., 2022; Pezzoli et al., 2023; Sun et al., 2016). Additionally, the thickness and degree of intrinsic functional connectivity of these regions are associated with better memory abilities in both superagers and typical older adults (Sun et al., 2016; Zhang et al., 2019). These findings are further supported by recent evidence showing high metabolic activity in both the hippocampus and the broader cingulate cortex in superagers (Borelli et al., 2021). The anterior MCC in particular has been previously described as a key region of a neural signature of superaging (Sun et al., 2016) and an "important region involved in the neurocircuitry of underlying successful aging" (Harrison et al., 2018), making it a potential imaging biomarker for resilience to age-related cognitive decline. Notably, however, Powell et al. found no evidence of this 'neural signature' of superaging.

The null imaging results reported by Powell et al. may be in part due to the parameters of magnetic resonance imaging (MRI) data acquisition, processing, and/or analysis. Specifically, MRI data analyzed in the Powell et al. study were collected using four different scanners that varied in field strengths (1.5 and 3 Tesla) and manufacturers. Higher field strength MRI generally yields an enhanced signal contrast between tissue compartments, which could result in larger regional gray matter morphometric estimates (by as much as ~30%; Buchanan et al., 2021). In group-level analyses of regional brain volumes, it is also a standard practice to control for total intracranial volume (i.e., head size), although this adjustment was not reported in Powell et al. Prior work employing vertex-wise analyses of surface-based MRI data have consistently identified between-group differences in MCC thickness; however, the precise anatomical location and spatial extent of such differences was somewhat variable from one study to another (Harrison et al., 2012, 2018; Katsumi et al., 2022; Sun et al., 2016). It is therefore possible that Powell et al.'s analytical approach based on anatomically-defined regions of interest might not have been sufficiently sensitive to characteristic neural differences between superagers and typical older adults. Altogether, these technical considerations are important to consider and carefully address for comparisons across studies to be more meaningful.

There are several outstanding issues that warrant clarifications in future studies of superaging. First, the vast majority of prior studies on superaging are cross-sectional in nature; more longitudinal studies are needed to investigate how aspects of cognition and brain integrity in superagers change over time relative to non-superagers. One study reported that superagers did not show performance decline on measures of episodic memory, attention, language, and executive function over a 18-month period (Gefen et al., 2014); another study showed that superagers had slower decline in episodic memory function over a 5-year period compared with typically-aging older adults (Harrison et al., 2018). Superagers were also ~70% less likely to receive a clinical diagnosis of mild cognitive impairment or dementia over a 8-year period than their cognitively normal counterparts, despite the similar proportion of amyloid-positive participants and *APOE* ε4 carriers in both samples (Dang et al., 2019). Interestingly, superagers and typical older adults show age- and AD-related cortical atrophy at comparable rates over 8 tears, suggesting that the former group may show resilience to these changes. More work is needed to better understand the trajectory of cognitive and brain aging in superagers vs. typical older adults and examine the role of other factors, including lifestyle, fitness, genetic, and social influences. In social domains, loneliness may be particularly important to consider because of its association with increased dementia risk, as highlighted by recent work in *International Psychogeriatrics* (Sutin et al., 2023).

Second, current evidence on superaging is largely based on samples of Western and highly educated individuals, limiting the generalizability of findings to the rest of the population. There is evidence, however, suggesting that culture and age interact to influence episodic memory and its mechanisms, including the trajectory of age-related decline (Lipnicki et al., 2017). As such, future work should characterize and compare superagers across cultures to better understand how cultural and societal values might modulate youthful memory function and brain integrity in late adulthood.

Third, neuroimaging studies of superaging have thus far primarily focused on examining anatomical features (e.g., gray matter volume/thickness, white matter integrity) and little is known about their brain function. Prior work on intrinsic functional connectivity estimated from resting-state functional MRI has revealed the involvement of the large-scale default mode network (including regions in the isocortico-hippocampal circuit) and the salience network (including frontoparietal and cingulate cortical regions) in differentiating superagers from typical

older adults (Zhang et al., 2019). Superagers also exhibit youthful brain activation patterns during episodic memory encoding and retrieval, which are associated with their memory performance (Katsumi et al., 2021). As more neuroimaging evidence becomes available, future work should integrate high-dimensional, multimodal imaging data to comprehensively characterize the unique properties of superagers' brains.

Taken together, Powell et al.'s findings highlight the importance of considering the definitional variability in interpreting the results of superaging studies. The study marks an important first step toward much needed harmonization of definitions of superaging in multi-site studies employing large and demographically diverse cohorts with the goal to better understand the phenomenon of superaging.

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