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Alzheimer's & Dementia

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

Comments about SuperAging and SuperAgers

Since the study by Katzman et al. [1], the finding that cognitively intact individuals may have significant amounts of Alzheimer's disease (AD) pathology has been a fertile source of studies. One way to understand this anomalous finding has been to consider cognitive reserve [2] Basically, both early- and later-life experiences, including education and other enrichment oriented activities, provide a buffer, not against neuropathology but against its impact on cognition. The twist in this study by Dang et al. [3] was that once pathology was evident in the form of Aβ deposition, cognition was not preserved over time.

This study and an equally important and complementary study published by this group in 2018 tell a consistent story [4]. To recapitulate, that paper, utilizing a group of SuperAgers defined psychometrically and a group of otherwise cognitively intact individuals from Australian Imaging, Biomarkers and Lifestyle study (identical to the 2019 groups), studied memory performance over a 9-year period. Briefly, the SuperAgers had higher baseline performance. When the groups were divided into Aβ+ and Aβ−, slope of performance over time in the SuperAger and control groups were similar. The Aβ+ group in both the control and SuperAger groups declined, whereas the Aβ− groups demonstrated increases in performance almost certainly due to practice effects. The memory construct was reasonable on the face of it (but see below). In the second study (2019), reviewed here, a similar pattern held, but this time with respect to magnetic resonance imaging volumetric measures, including total gray matter and hippocampus, with one small difference. The Aβ− groups showed small volume decreases over time consistent with aging effects. In short, being a SuperAger was not neuroprotective. Given similarities in slopes of decline, it was reasonably proposed their baseline elevation simply delayed the point at which a clinical of mild cognitive impairment or AD was reached. This was born out in differences in incident mild cognitive impairment and AD between the SuperAger and control groups, the former being lower (with an OR = .19 for mild cognitive impairment).

Now for some comments. These can be grouped as to relating to what is happening to the right of baseline and to the left.

Superficially, Aβ aggregation appears to be the culprit here. It was likely driven by apolipoprotein E (*APOE*) ε4 genotype given the high and disproportionate number of e4 carriers in this group. However, as we have shown in ADNI, accelerating slopes of Aβ and tau levels may be relatively coincident [5]. Thus, aggregation of tau may be playing a significant role in decline. Second, and again to the right of the baseline, there is misalignment between memory improvement over time in the Aβ− groups and gray matter decreases in this same group. This nicely illustrates the confounding effect of practice effects in the memory domain: There is improvement even when there is demonstrable gray matter age-associated atrophy.

An unanswered question is what has happened to the left of baseline. Why are SuperAgers superior? One possibility relates to neuroprotective factors. *APOE* ε2 reduces risk of AD by nearly 50%. As we and others have shown, it is known to have multiple neurobiological pathways identified in the postmortem cortex toward neuroprotection and at the biomarker level, has an "anti-AD" CSF Aβ and p-tau profile [6]. Is it possible that a disproportionate number of individuals in the Aβ− SuperAgers were e2 carriers? This could easily be examined.

Similarly, the Australian Imaging, Biomasrkers and Lifestyle study group has conducted a compelling series of studies on BDNF val/met genotype and serum bdnf levels in Australian Imaging, Biomasrkers and Lifestyle study and DIAN (e.g., [7]). Do either of these factors play a role in SuperAger baseline performance?

The cutoff for SuperAgers is generous and is dependent on US norms. It resulted in nearly a 30/70 split before matching (and a 50/50 split in matched subjects). Perhaps, a more rigorous cutpoint would have been more informative.

Use of binary education cutoff for matching was somewhat unrefined. Perhaps, treating education as a continuous variable would have impacted results. This being said premorbid IQ differed trivially between the matched groups. I would like to see the education level and premorbid IQ of the SuperAgers compared with the remaining total control group.

On a more technical note, the 2018 study utilizes the California Verbal Learning Test (CVLT) in the memory construct under examination. Recall that the CVLT was used to separate the groups. In a sense this is tautological. Perhaps, the analyses could be rerun without CVLT in the

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memory domain and thus examine Logical Memory (the other test in this construct) alone.

Is it possible the SuperAgers may not be SuperAgers but CVLT savants, a heretofore unknown diagnosis. This comment is meant to be more than facile. Just as healthy populations reliably demonstrate impairment on 1-2 neurocognitive tests in a neurocognitive battery, healthy individuals may also do well on a test because of stochastic factors. As noted, the CVLT drives the memory domain that includes only a single other test (Logical Memory). In this view, there is little super about SuperAgers, not on neural systems, not on resilience, and not on education or intelligence. Maybe the term LuckyAgers would be more apt for this sample.

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