

SuperAgers: Insights Into the Brains of 80+-Year-Old Memory Superstars

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By Arline Kaplan



Despite the prevalent perception that cognitive decline in the aged population is inevitable, researchers with Northwestern University's SuperAging Project are finding that "excellent memory capacity in late life is a biological possibility."

A recent study by Rogalski and colleagues¹ identified an elite group of individuals 80 years and older who did as well or better on episodic memory tests as healthy individuals who were 20 to 30 years younger. The researchers call them "SuperAgers."

Emily Rogalski, PhD, lead author of the recent study of 12 SuperAgers and a Research Assistant Professor at Northwestern's Cognitive Neurology and Alzheimer's Disease Center (CNADC), explained that the multidisciplinary center is 1 of 27 nationally funded Alzheimer disease centers. The center's multidisciplinary team follows individuals who have Alzheimer disease (AD) and other dementias but also follows healthy individuals.

As with other National Institute on Aging-supported centers, the CNADC team "does a lot of research on dementia, on what goes wrong with the brain, and on how we can we fix it," Rogalski told *Psychiatric Times*. "But we decided to look at things from the flip side and to ask if there are individuals who are able to resist memory loss and who have outstanding memory performance in old age."

Rogalski said she and others seek to unlock the secrets of SuperAgers' youthful brains. Their hope is that what they learn may "inform our strategies for improving quality of life for the elderly and for combating AD."

"The study started as a proof of concept, and we have been successful at identifying individuals aged 80 years and older who have memory performance at least as good as 50-year-olds," Rogalski said. "They also perform at least in the average range for their age in other domains of cognition."

The research team, according to Rogalski, recruits healthy individuals 80 years and older who think they have good memories from the CNADC and from the Chicago area through community lectures, referrals, and flyers.

"Typically, individuals who are interested in participating call us and go through a phone screening process where we give some brief cognitive tests that provide us a good idea of whether they will meet the criteria for enrollment," she said.

Those who might meet the enrollment criteria, Rogalski added, come to the center for 2- to 3-day visits. They undergo additional cognitive testing and are questioned about their personality and medical and family history. They donate blood and undergo an MRI brain scan. They sign up for the longitudinal study, and they return every 18 months.

Of the healthy individuals 80 and older who think they have an outstanding memory, only about 10% qualify as "SuperAgers," Rogalski said. To be designated SuperAgers, individuals are required to perform at or above average normative values for individuals in their 50s and 60s on the delayed recall scores of the Rey Auditory Verbal Learning Test. They must also perform within 1 standard deviation of the average range for their age and education for the nonmemory measures, according to published normative values based on age, gender, and race/ethnicity.

What's special about them

Researchers are seeking to identify factors that may contribute to the outstanding memory performance of SuperAgers.

In an initial study published in the *Journal of the International Neuropsychological Society*,² the Northwestern team sought to determine whether SuperAgers were resistant to age-related loss of cortical brain volume. The study

included 12 identified SuperAgers (average age of 84) from the Chicago area, 10 normally aging elderly participants (average age of 83.1), and 14 middle-aged participants (average age of 57.9).

“We asked a very simple question for the study: if individuals have outstanding memory, do their brains look more like their cognitively matched peers or do they look more like their age-matched peers?” Rogalski said. “We found the brains of SuperAgers looked more like those of the 50-year-olds than those of their age-matched peers. There was no significant cortical thinning or atrophy in the SuperAgers compared with the individuals 20 to 30 years their junior.”

In addition, an area located in the **left anterior cingulate** was significantly thicker in SuperAgers than in the middle-aged control group by nearly 0.8 mm on average.

“The anterior cingulate is important for **attention as well as many other emotional- and higher-order functions**,” she said. “So perhaps that is what is helping to keep their memories so strong in old age.”

The findings were “pretty remarkable,” Rogalski said, “since extensive aging research demonstrates that increasing age is associated with decline in memory performance and atrophy of the cortex. Instead, initial research from our team found that among SuperAgers, the integrity of the cortex and memory performance were maintained.”

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Other factors

Beyond looking at the **structural imaging features of SuperAgers**, the team is exploring other factors that might contribute to superaging, such as **genetics and pathology**.

Participants in the recent study provided blood samples from which DNA was extracted for genotyping. *ApoE* was targeted for initial investigation because the $\epsilon 4$ allele of this gene is the most extensively documented genetic risk factor of AD.

“We found that the incidence of the $\epsilon 4$ allele in the SuperAgers was lower than that of the healthy control population. So there may be some genetic factors that are playing a role,” Rogalski said. Of the 12 SuperAgers included, only 1 (8%) had an $\epsilon 4$ allele ($\epsilon 3$, $\epsilon 4$) and the others had the $\epsilon 3$, $\epsilon 3$ pattern, which is the most common genotype in the general population.

The diagnosis of AD requires the postmortem detection of amyloid plaques and neurofibrillary tangles in specific densities and distributions, according to Rogalski.

“We asked if there is less Alzheimer pathology in the brains of SuperAgers; the answer is yes so far in a few cases we have looked at. These individuals seem to be resistant to losing brain integrity and seem to have less Alzheimer pathology,” she said. While examining the postmortem material of the SuperAgers, the researchers were surprised by the prominence of von Economo neurons (also called spindle neurons), which Rogalski said are found only in higher-order species and in 2 regions of the brain, one of which is the anterior cingulate area. The preliminary findings that these neurons may be more numerous in SuperAgers may be related to the equally puzzling finding of the increased thickness of cingulate cortex in this group, the research team reported in the study findings.

Armed with the results of the study of the initial cohort of 12 SuperAgers, the team is continuing to enroll individuals in its “Super-Aging” research study.

“We are following the original group of 12 SuperAgers longitudinally as well as new enrollees. All of them have agreed to donate their brain at the time of death, so we are able to investigate the cellular aspects of health,” Rogalski said.

Another 28 SuperAgers have been identified so far. For that group, the researchers will continue to ask some of the same questions but have also broadened their investigations.

“We are also looking at how long SuperAgers are able to maintain good cognitive performance over time as well as examining the health of their cortical integrity over time.”

90+-Year-Old “Stars”



In an interview with *Psychiatric Times*, neurologist Claudia Kawas, MD, AI and Trish Nichols Chair in Clinical Neuroscience and Professor of Neurobiology & Behavior and Neurology at the University of California, Irvine (UCI), was asked to comment on the Rogalski study. Kawas is a principal investigator on the 90+ Study,⁶ a population-based sample of the oldest-old that has enrolled more than 1600 individuals during the past decade to study both good and bad outcomes in extreme aging. Over the past decade, Kawas and her team received \$15 million from the NIH to continue the study.

Kawas wondered whether “the SuperAgers always had larger cortical volumes or whether they decline less rapidly than their colleagues.” She also pondered whether the research findings of Rogalski and colleagues can be replicated in another, larger sample of SuperAgers.

Like Rogalski, Kawas said she and her team have encountered some “star” performers on episodic memory tests among the 90+-year-olds they have studied, “at least on the level of remembering virtually all the words on the lists we gave them.”

Kawas and her team are seeking to determine factors associated with longevity; to focus on the epidemiology of dementia in the oldest-old; to determine rates of cognitive and functional decline in the oldest-old and look at clinical pathological correlations with memory loss and dementia; and to identify modifiable risk factors for dementia and death.

They have published several articles on lifestyle factors and mortality. They found, for example, that maintaining or gaining weight was associated with greater longevity, while intake or supplementation with vitamins E, C, and A was not.

“We do a lot of epidemiological studies, including risk factors and incidence rates for dementia and disability,” Kawas said. The team found that more than 40% of people 90 years and older suffer from dementia, while almost 80% are disabled.⁴ Both dementia and disability are more common in women than in men.

Other studies, she said, involve longitudinal follow-up with clinical pathological correlation whenever possible. Her team recently initiated imaging studies with PET and MRI.^{5,6}

“Essentially we found that half of demented participants in their 90s have AD pathology—but so do half of the non-demented,” she said. “Recently, we published a manuscript showing that rates of decline based on PET amyloid imaging (florbetapir), amyloid-positive subjects declined cognitively more than amyloidnegative.”

Asked whether cognitive decline in the aged population is inevitable, Kawas responded: “I don’t know if it is inevitable or not, but I do know that humans do it with amazing variability. I want to know the factors that might help more of us do it at the better end of the spectrum.”

Rogalski also noted, “We are beginning to explore other cellular and genetic factors that may be playing a role, as well as lifestyle choices, personality, and psychosocial factors that may influence their memory.”

With regard to possible lifestyle factors, Rogalski told a *Chicago Sun Times*’ reporter that SuperAgers “may not live pristine lifestyles as far as exercise and diet. Some of them are very interested in exercise and diet, while others are using a walker or are less active. Still others have been smoking a pack of cigarettes a day for 20 years.”³

The researchers also are not finding evidence to suggest that the SuperAgers have started from a higher baseline than others, Rogalski said.

“These are not savants who can remember what they were doing on a specific date 40 years ago,” she said. “These are normal, everyday people who have been able to avoid cognitive decline, and they aren’t particularly well educated. Not everyone in our study was a doctor or lawyer. In fact, many of them just had a high school education.”