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EDITORIAL

Successful cognitive aging

What the oldest-old can teach us about resistance and resilience

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Page 335

Over the past century, we have witnessed a remarkable extension of human life expectancy by >27 years. Reflecting this accomplishment, people ≥90 years of age are now the fastest-growing segment of the population in most of the world. Indeed, more than half of all children born today in developed countries are expected to live to 100 years of age or beyond,[1] and it is remarkable how little we know about these pioneers of aging. Biomedical research tends to focus on disease and poor outcomes, but the oldest-old individuals who have reached extreme age with preserved cognitive health present an unparalleled opportunity to investigate factors that may promote successful cognitive aging throughout the lifespan, even in the presence of neuropathologic changes associated with cognitive loss and dementia.

In this issue of *Neurology*, Snitz et al.[2] examine a broad array of long-term predictors of low β-amyloid (Aβ) pathology burden (resistance), maintenance of cognitive function, and maintenance of cognitive function in the presence of amyloid pathology (resilience). The study was conducted in a unique cohort of 100 participants (mean age 92 years) from the Imaging Sub-Study of the Gingko Evaluation of Memory Neuroimaging Study (GEMS) who have extensive information and more than a decade of longitudinal follow-up (imaging and cognitive status). The results show that *APOEε2* and lower pulse pressure are related to resistance to Aβ pathology, while baseline cognitive test scores predict cognitive status. Baseline cognitive scores also predicted normal cognition in Aβ-positive individuals, along with never smoking. In an examination of lifestyle factors in relation to longitudinal cognitive change, paid work engagement and life satisfaction predicted slower cognitive decline. The results of this exploratory study are potentially important in terms of our scientific understanding of the maintenance of cognitive health with aging, and they add to the current literature of resistance and resilience, particularly for the oldest old.

A wealth of investigations over the years have shown that better cognitive performance is associated with less risk of cognitive decline and incident dementia in the elderly.[3,4] With advances in technology, more recent studies, including this one, have shown that better cognitive performance is also associated with less risk of decline in individuals with Aβ positivity. An important question to consider in studies of resilience is whether good performance in an individual with Aβ positivity reflects resilience to amyloid or merely an earlier stage of the Alzheimer disease (AD) process, given that individuals typically demonstrate amyloid positivity for a decade or more before the development of cognitive symptoms.[5] The 14-year window of this longitudinal study supports the notion that these individuals may indeed be resilient. Further research is necessary to understand the biological underpinnings and factors that contribute to this resilience.

Although resilience is an important consideration for successful aging, resistance to Aβ deposition at this advanced age is particularly intriguing. In this study, 2 factors emerged: pulse pressure and *APOE* genotype, the strongest AD genetic susceptibility factor related to amyloid deposition and AD. Both areas deserve replication and additional research as we seek to identify mechanisms and potential targets to promote resistance in all of us. As the authors pointed out, there is growing evidence that *APOE* may have effects independently of or downstream to

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amyloid that are relevant to cognitive preservation. Although genetics are not modifiable at the moment, pulse pressure may represent a modifiable risk factor and should be an area of intense research.

Like all studies, the current study has limitations. Currently, all investigations like this study that use neuroimaging to examine resistance and resilience are limited to the examination of AD-related pathology. However, we know that multiple neuropathologic abnormalities are very common at very advanced ages.[6–8] It is possible that the apparent resilience to AD pathology established by imaging merely reflects resistance to other non-AD pathologies, including hippocampal sclerosis, microvascular disease, and Lewy bodies.[9] To fully understand successful cognitive aging, it will be crucial to extend the study of resistance and resilience to all important dementia-related pathologies. Lastly, the research participants in this investigation were primarily male, white, and well educated, which limits generalizability to more diverse populations. Indeed, approximately three-fourths of all individuals >90 years of age are women, and minority oldest old is a rapidly growing group and profoundly understudied.

The oldest old have a lot to teach us. Extending life expectancy came at a price: we extended disabled life more than able life. Maintaining cognitive abilities throughout the lifespan would have staggering public health benefits and is ultimately the goal for all of us. With the help of oldest-old individuals, we can learn the biological underpinnings of successful aging and potential strategies for resistance and resilience.[10] The oldest old will help us learn how to add life to the growing number of years we have.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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