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A Call for New Thoughts About What Might Influence Human Brain Aging:

Aging, Apolipoprotein E, and Amyloid

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"The wiser mind mourns less for what age takes away than what it leaves behind."

William Wordsworth, *The Fountain*

As a greater proportion of the world's population live beyond age 65 years, there is increasing awareness of age-related differences in cognitive ability and a rising interest in finding ways to maintain healthy brain aging with the hope to avoid dementia. Although conventional wisdom stresses the inevitable decline of cognitive ability with age, seminal work by Wilson et al[1] finds that individual trajectories of cognitive ability vary greatly, suggesting that at least some of the age-related differences in cognitive ability are due to incipient disease. Conventional wisdom also stresses that incipient or clinically expressed Alzheimer disease (AD) explains most cognitive decline and incident dementia among older individuals. The negative impact of incipient AD on cognitive ability among apparently cognitively normal older individuals is further supported by the long prodromal period of the AD process. The advent of in vivo amyloid imaging (and even eventually tau imaging) has stimulated intense interest regarding the role of incipient AD in relationship to cognitive aging. Early reports suggest a strong relationship between memory performance and cortical amyloid retention in a group of individuals with various degrees of cognitive ability. Later studies also found that increased cerebral amyloid burden, which is highly associated with age and the apolipoprotein E ε4 (*APOE ε4*) genotype[2] among cognitively normal individuals, is associated with subtle declines in cognitive performance[3] and increased risk for future dementia.[4] This work and the increasing availability of biological markers of AD pathology have led to a proposed biological cascade model of AD[5] and reevaluation of diagnostic criteria for AD.[6] If one ascribes religiously to the concept that a large proportion of cognitive differences with age are driven by incipient disease, then one might expect that memory performance–a cognitive ability that changes most dramatically with age and is common to AD–would follow increasing levels of associated cerebral amyloid and be strongly associated with hippocampal atrophy. In their article, Jack et al[7] present new

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information that challenges the notion that amyloid accumulation explains memory performance across the entire age range. Importantly, this work does not only address the likely highly significant impact of cerebral amyloid accumulation on dementia risk, but also extends current knowledge relating to the impact of the aging process across the spectrum of ages 30 to 95 years to brain structure, amyloid accumulation, and memory performance among cognitively normal individuals.

Their study[7] details cross-sectional associations between age; memory performance using the auditory-verbal learning test, a common memory task; hippocampal volume; and the extent of cerebral amyloidosis for a group of more than 1200 men and women, ranging from age 30 to 95 years. A number of important findings come from this seminal study. One particularly striking result was the rather dramatic changes in both hippocampal volume and memory performance seen before age 65 years and before the age when the prevalence of extensive cortical amyloid burden is increasing. Moreover, the apparent slope of memory decline appears to increase after age 65 years, in conjunction with or slightly before an inflection and increasing prevalence of extensive cerebral amyloid burden. While the authors remind us that we cannot infer causality from cross-sectional studies, this remarkable study prompts the question as to what may cause hippocampal and memory changes in early life.

If one tenaciously holds to the notion that the insidious consequences of other diseases may be contributing to these earlier differences, vascular brain injury is an obvious candidate. Vascular risk factors, such as diabetes mellitus, are associated with subtle cognitive impairment among individuals aged 47 to 57 years[8] and hypertension is associated with significantly greater cerebral atrophy among individuals 40 years on average.[9] Moreover, numerous studies of middle-life vascular risk factors have found that they increase the risk for later-life dementia and are associated with accelerated brain injury.[10] In addition, measures of vascular brain injury significantly increase the risk for later-life cognitive impairment, dementia, stroke, and even mortality.[11] These data support the notion that vascular brain injury may begin early in life in a subset of affected individuals that affects both cognition and brain structure. While the high prevalence of hypertension, which is approximately 11% for individuals between 18 and 40 years but increases to 40% of US adults 45 to 64 years,[12] is highly suggestive as a cause for the observed differences in cognition and hippocampal volume. However, reported studies have found that vascular risk factors are more likely to lead to generalized cerebral atrophy[9] and nonmemory cognitive impairments,[8] which contrast with the findings of Jack et al[7] in this issue of *JAMA Neurology*. Therefore, while vascular risk factors likely contribute to some of the cognitive impairments known to occur with normal aging, they do not fully overlap with the findings reported by Jack et al.[7]

To what other processes then can we ascribe the differences in hippocampal volume and memory performance found before age 60 years? Genetic influences certainly play a role. Sex has an overwhelming genetic influence and findings shown in this study are consistent with other published findings of sex differences in brain structure and cognition. Consistent with these other studies, Jack et al[7] show significant sex differences in memory and hippocampal volume across the age span, with differences in memory performance being

particularly substantial earlier in life with men doing more poorly on tests of memory performance and having smaller hippocampal volumes in proportion to head size than women. However, the risk for late-life dementia does not favor a higher prevalence of dementia among men, raising further interesting questions about the role of early aging sex differences in memory performance and brain atrophy and the risk for later-life dementia. Apolipoprotein E is another major genetic factor and the results from the study by Jack et al[7] and others confirm the profound effect of *APOE ε4* genotype on amyloid retention beyond age 70 years. Yet, unlike the effect of the *APOE ε4* genotype on gray matter metabolism throughout the life span,[13] the impact of *APOE ε4* on hippocampus and memory performance appear more directly related to co-occurring AD degeneration[14] with the same later age at onset. In addition to the evidence of major gene effects, twin and family studies have found high heritability coefficients for memory performance and brain and hippocampal volume among older as well as younger individuals. Genome-wide association studies in large community-based studies of patients ranging from age 30 to 90 years have found significant associations between hippocampal volume and non-AD genes, suggesting independent genetic effects[15] that may indicate other biological pathways that could explain age-related differences. Similar genetic association studies with memory performance among cognitively normal older individuals also have been significant.[16] However, the impact of these genetic polymorphisms is relatively small (eg, 0.2 SD for the hippocampus[17]) and, again, cannot fully explain the findings seen by Jack et al.[7]

As is often the case for new scientific findings, we are left with more questions than clear answers. Cognitive neuroscientists have established a host of theories that describe differences in cognitive performance in young and middle-aged individuals,[18] which provide a strong foundation for mechanistic research related to the early aging of the brain. Further genetic and animal model studies, particularly of nonhuman primates,[19] are likely to elucidate specific cell types and cortical networks that change most dramatically during the first 40 to 50 years of life. Understanding the basic biology of these early processes are likely to substantially inform us about ways in which we can maintain cognitive health and optimize resistance to late-life dementia. However, such work requires the necessary motivation found by seminal work, such as that of Jack et al,[7] which tell us where and when to investigate these processes. Establishing what is normal[20] creates avenues for new research, increasing the likelihood of discovering novel therapeutics for late-life disease states, which is a laudable goal indeed!

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