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At the crossroads: Preclinical AD, normal brain aging, and cognitive reserve

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The advent of methods to measure putative biomarkers of Alzheimer's disease (AD) *in vivo* has greatly broadened understanding of the temporal evolution and clinical significance of AD pathophysiology.¹ Importantly, it is now widely accepted that biomarkers of AD become abnormal long before clinical symptoms are manifest. This development has led to the formulation of research guidelines for preclinical AD by expert panels such as the National Institute on Aging-Alzheimer's Association (NIA-AA)² and the International Working Group.³ In the NIA-AA scheme,² preclinical AD segregates into three contiguous stages. Stage 1 is characterized by brain amyloidosis alone, Stage 2 is amyloidosis plus neurodegeneration, whereas Stage 3 includes the features of Stage 2 plus subtle cognitive changes. Subsequently, a Stage 0 was proposed⁴ to capture asymptomatic persons who were devoid of cerebral amyloidosis, neurodegeneration, and cognitive changes and, therefore, were yet to enter the AD pathophysiological pathway.

Because the NIA-AA preclinical AD criteria do not provide for the classification of cognitively normal adults who exhibit neurodegenerative changes in the absence of amyloidosis, a complementary two-feature biomarker classification system was recently proposed by Jack and colleagues.⁵ In this taxonomy, each individual is labeled as being positive (+) or negative (–) for cerebral amyloidosis (A) and neurodegeneration (N), resulting in four mutually exclusive groups: **A–N–** which corresponds to NIA-AA preclinical AD Stage 0, **A–N+** which corresponds to suspected non-Alzheimer pathophysiology (SNAP), **A+N–** which corresponds to NIA-AA preclinical AD Stage 1, and **A+N+** which corresponds to NIA-AA preclinical AD Stages 2 and 3.

In this issue of *The Lancet Neurology*, Jack et al.⁶ assessed age-specific frequencies of the four **A/N** groups in a population-based sample of asymptomatic adults aged 50–89 years. They found that the population frequency of **A–N–** was virtually 100% between ages 50 and 59, and then decreased to about 17% by age 89. The frequency of **A–N+** was close to zero

before age 60 and thereafter increased to 24% by age 89. Frequency of A+N⁻ was zero at age 50, then increased to 28% by age 74 before decreasing to 17% by age 89. The frequency of A+N⁺ was essentially zero before age 65 and thereafter increased to about 42% by age 89. Not surprisingly,⁷ carriers of the apolipoprotein E ε4 allele were overrepresented in the A+N⁻ and A+N⁺ groups. An important theoretical development in this paper is the proposal of three hypothetical, pathological sequences that cognitively normal persons might follow: first is A-N⁻ to A+N⁻ to A+N⁺, which is the prototypical AD cascade, second is A-N⁻ to A-N⁺ to A+N⁺, which represents someone who first develops SNAP and later enters the AD pathophysiological pathway, and third is A-N⁻ to A-N⁺, which represents individuals for whom SNAP is a pathophysiological end state.

Overall, this is clearly important work and furthers our understanding of the prevalence of preclinical AD in the community which, in turn, has several practical applications including the effective design of clinical trials in this stage of AD that has been dubbed a “crucial window of opportunity” for arresting the global threat posed by AD.² Even so, because the study is cross-sectional, some important aspects of the changes in the age-specific frequencies of the A/N groups will perforce remain opaque to us, such as how the frequencies are influenced by inter-group transitions, incident cognitive impairment, mortality, and similar competing factors. Prospective studies will be necessary for answering this question, as well as determining the long-term prognostic utility of this scheme as regards progression to symptomatic AD.

Another important consideration raised by this study deals with the borderland between preclinical AD and normal brain aging. The data reported by Jack et al.⁶ suggest that, by age 89, about 83% of otherwise healthy older adults will have AD-like levels of amyloidosis and/or neurodegeneration. On the one hand, this finding is consistent with the known co-variation between advanced age and AD pathology.⁸ On the other hand, it highlights the inherent difficulty with disambiguating normal aging from pathological aging. If indeed the accrual of cerebral pathology is the norm rather than the exception in the later decades of life, then applying the label “normal aging” to the subset of, say, the oldest-old who lack such pathologies would be a contradiction in terms.

Perhaps the distinction between normal and pathological aging more properly pivots on the capacity/lack thereof to maintain optimal cognitive function despite harboring pathogenic brain lesions rather than on the mere absence/presence of such pathologies. This “discontinuity” between cerebral pathology and clinical symptoms has become an active area of inquiry, and goes by diverse monikers including cognitive reserve, brain reserve, compensation, and resilience.⁹ A less studied component of reserve deals with the modulation of “expected” age-pathology associations by sundry life experiences such as physical activity and education. For example, in a recent work from our group¹⁰ we showed that, among asymptomatic, at-risk, late-middle-aged adults (the Wisconsin Registry for Alzheimer’s Prevention), those who were physically active exhibited attenuated age-related alterations in amyloid-β burden, glucose metabolism, hippocampal volume, and memory test scores compared with the physically inactive.¹⁰ Additional yet unpublished work from our group similarly reveal that high educational attainment (> 16 years of schooling) is differentially associated with a diminution of the deleterious influence of age on

cerebrospinal fluid levels of total tau, phosphorylated tau, and their respective ratios with amyloid- β 42. These findings raise the sanguine possibility that certain life experiences might play a central role in the secondary prevention of AD. As noted earlier, the two-feature biomarker scheme proposed by Jack et al.⁶ will be foundational to the design of trials to more rigorously test whether and how life experience modulates the AD pathophysiological cascade in preclinical AD.

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