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At the crossroads of preclinical AD and normal brain ageing

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The advent of methods to measure putative biomarkers of Alzheimer's disease (AD) in vivo has greatly broadened our 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 schema,[2] preclinical AD segregates into three contiguous stages. Stage 1 is characterised by brain β-amyloidosis alone, stage 2 by amyloidosis plus neurodegeneration, and stage 3 includes the features of stage 2 plus subtle cognitive changes. Subsequently, a stage 0 was proposed[4] to capture asymptomatic people who were devoid of cerebral amyloidosis, neurodegeneration, and cognitive changes and, therefore, were yet to enter the AD pathophysiological pathway.

Because the NIA–AA criteria for preclinical AD do not provide for the classification of asymptomatic adults who have neurodegenerative changes in the absence of amyloidosis, Clifford Jack and colleagues[5] proposed a complementary two-feature biomarker classification system. In this taxonomy, each individual is labelled 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 stage 0; A^-N^+, which corresponds to suspected non-Alzheimer's pathophysiology (SNAP), A^+N^-, which corresponds to NIA–AA preclinical stage 1; and A^+N^+, which corresponds to NIA–AA preclinical stages 2 and 3.

In *The Lancet Neurology*, Jack and colleagues[6] assessed age-specific frequencies of these four groups in a population-based sample of 985 asymptomatic adults aged 50–89 years. The estimated population frequency of A^-N^- was 100% at age 50 years and then decreased to 17% (95% CI 11–24) by age 89. The frequency of A^-N^+ increased from age 60 years to 24% (16–34) by age 89 years, whereas that of A^+N^- increased to 28% (24–32) by age 74 years and then decreased to 17% (11–25) by age 89 years. The frequency of A^+N^+ increased from age 65 years to 42% (31–52) by age 89 years. Unsurprisingly,[7] carriers of the *APOE* 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 people with normal cognitive function might follow: A^-N^- to A^+N^- to A^+N^+, which is the prototypical AD cascade; A^-N^- to A^-N^+ to A^+N^+, which represents someone who first develops SNAP and later enters the AD pathophysiological pathway; and A^-N^- to A^-N^+, which represents individuals for whom SNAP is a pathophysiological end state.

Overall, Jack and colleagues' study[6] is clearly important work and furthers our understanding of the prevalence of preclinical AD in the community. The findings have several practical applications, including the design of clinical trials in preclinical AD, which has been described as a crucial window of opportunity for intervention.[2] However, because the study was cross-sectional, some important features of the changes in age-specific frequencies of the A/N groups remain opaque, such as how the frequencies are affected by intergroup transitions, incident cognitive impairment, study attrition, mortality, and similar competing factors. Prospective studies will be necessary to identify how the frequencies are affected by such competing factors, as well as to determine the long-term prognostic usefulness of this schema with respect to progression to symptomatic AD.

Another important issue raised by this study is the borderland between preclinical AD and normal brain

ageing. The data reported by Jack and colleagues[6] suggest that, by age 89 years, about 83% of otherwise healthy adults will have AD-like levels of amyloidosis, neurodegeneration, or both. This finding is consistent with the known covariation between advanced age and AD-associated pathological changes,[8] but emphasises the inherent difficulty in distinguishing normal from pathological ageing. If indeed the accrual of cerebral pathological changes is the norm rather than the exception in the later decades of life, then applying the label of normal ageing to, for example, the subset of very old people who do not have such pathological changes, would be a contradiction in terms.

Perhaps the distinction between normal and pathological ageing more properly pivots on the capacity to maintain optimum cognitive function despite harbouring pathogenic brain lesions, rather than on the mere absence or presence of such pathological changes. This discontinuity between cerebral pathological changes 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 associations between age and pathological changes by sundry life experiences such as physical activity and mental stimulation. For example, our group[10] has shown that, among asymptomatic, at-risk, late-middle-aged adults in the Wisconsin Registry for Alzheimer's Prevention, those who were physically active had attenuated age-related alterations in amyloid-β burden, glucose metabolism, hippocampal volume, and memory test scores compared with the physically inactive. Such findings raise the sanguine possibility that some life experiences might have a central role in the secondary prevention of Alzheimer's disease. The two-feature biomarker schema proposed by Jack and colleagues[6] will be foundational to the design of trials to test more rigorously whether and how life experience modulates the pathophysiological cascade in preclinical AD.

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Corrections

Furman JM, Marcus DA, Balaban CD. Vestibular migraine: clinical aspects and pathophysiology. Lancet Neurol *2013;* **12:** *706–15*—In the epidemiology section, the reported prevalence of vestibular migraine in women aged 40–54 years should be 5% and not 1%. This correction has been made to the online version as of Sept 15.