



Long-term forgetting in preclinical Alzheimer's disease

See [Articles](#) page 123

Alzheimer's disease is characterised by progressive pathophysiological changes that correspond roughly to preclinical (ie, cognitively unimpaired), mild cognitive impairment, and dementia stages.¹ Biomarkers continue to be developed, tested, and used to detect and track the pathophysiological manifestations of this disease. Although neuropsychological tests, clinical ratings, and composite cognitive test scores have shown initial promise,²⁻⁵ the field would benefit from additional ways to detect and track cognitive, behavioural, and functional manifestations of Alzheimer's disease with optimal power, ease, and availability, particularly in the preclinical and early clinical stages.

In this issue of *The Lancet Neurology*, Philip Weston and colleagues⁶ show the promise of a baseline and 7-day follow-up assessment strategy to measure accelerated long-term forgetting in presymptomatic Alzheimer's disease. 35 cognitively unimpaired autosomal dominant Alzheimer's disease mutation carriers and non-carriers were studied on average 7 years before their affected parents' age at symptom onset. Standard 15-item word list, short story, and complex figure learning and recall memory tests were done during an initial in-person assessment. Recall and recognition memory tests were done during a 7-day follow-up telephone call. Although the groups did not differ in their learning or 30-min recall memory scores, carriers did less well in measures of recall and recognition memory 7 days later. 7-day forgetting was associated with subjective memory concerns and proximity to age at symptom onset in the carriers. On the basis of these findings, the authors suggest that accelerated long-term forgetting might provide a more sensitive indicator of cognitive decline than do standard learning or 30-min memory tests in presymptomatic Alzheimer's disease; they suggest that accelerated long-term forgetting reflects an early decline in mediated memory consolidation and associated Alzheimer's disease pathology in the hippocampus, contributes to some of the earliest subjective memory concerns in at-risk persons, and has the potential to help evaluate preclinical treatments.⁶

Additional research is needed, not only to confirm the study findings in the presymptomatic stages of autosomal dominant early-onset Alzheimer's disease, but also to show generalisability to the preclinical stages

of late-onset disease and to consider how these results might be affected by ageing and other age-related disorders. Additional studies are also needed to clarify the extent to which accelerated long-term forgetting is related to biomarker measurements of amyloid burden, tau, and neurodegenerative pathology, other preclinical cognitive changes, and subsequent clinical progression. Refinements in the long-term forgetting framework might be needed to extend the findings of this study to later Alzheimer's disease stages, account for any initial learning and memory declines, minimise potentially confounding rehearsal and learning effects associated with longitudinal assessments, and provide an indicator of progressive cognitive decline that could be used as an endpoint in preclinical trials. Refinements to the framework might also be needed to minimise participant burden in longitudinal studies and preclinical Alzheimer's disease trials and support the study of long-term forgetting in observational studies and therapeutic trials.

Interest in use of mobile and other digital technologies to detect and track cognitive, behavioural, and functional changes with greater ease, real-world value, and statistical power is growing, and there could be a chance to leverage these technologies in assessment of long-term forgetting.⁷ This elegant study illustrates the opportunity now at hand to develop, test, and use new methods to detect and track the earliest cognitive changes associated with Alzheimer's disease, monitor a person's risk, and help evaluate promising prevention therapies.

Eric M Reiman

Banner Alzheimer's Institute, Phoenix, AZ 85006, USA
eric.reiman@bannerhealth.com.

I declare no competing interests.

Copyright © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

- 1 Sperlberg RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; **7**: 280-92.
- 2 Caselli RJ, Dueck AC, Osborne D, et al. Longitudinal modeling of age-related memory decline and the APOE ε4 effect. *N Engl J Med* 2009; **361**: 255-63.
- 3 Langbaum JB, Hendrix S, Ayutyanont N, et al. An empirically derived composite test score with improved power to track and evaluate treatments for preclinical Alzheimer's disease. *Alzheimers Dement* 2014; **10**: 666-74.