

Letter to the editor:

Impaired familiarity in individuals at risk for Alzheimer's disease: Commentary on
Schoemaker et al. (2016)

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Interventions aiming at postponing or preventing the development of Alzheimer's dementia (AD) should be implemented before the first clinical symptoms. It is therefore critical to identify individuals with incipient AD. The most inexpensive and non-invasive way to achieve this goal is the use of cognitive tests that are sensitive to initial AD cerebral pathology. More specifically, the earliest cognitive deficit should be one that affects the specific function that is supported by the entorhinal and perirhinal cortices where neurofibrillary tangles start to accumulate [1]. Recent advances in cognitive neuroscience indicate that the entorhinal and perirhinal areas play a critical role in familiarity-based memory [2], the feeling that some information has been encountered before. This function contrasts with recollection, in which one recalls qualitative details about the encounter with the information.

Although compelling and theoretically founded, the hypothesis that impaired familiarity may be a very early cognitive marker of AD has not been much investigated and led to inconsistent findings [for reviews, 3, 4]. Recently, Schoemaker, Poirier, Escobar, Gauthier, & Pruessner (2016, *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring*, 2, 132-139) addressed this hypothesis by testing cognitively healthy individuals who carry or not the $\epsilon 4$ allele of the APOE gene. In this study, 21 carriers of APOE $\epsilon 4$ (at risk for AD) and 60 non-carriers performed a memory task in which they studied pictures of faces under two conditions that differed in terms of the spatial location of the face, the color of the background, and the judgement to make about each face. Then, participants had to recognize the faces studied under the two conditions among new faces. For each face, they had to indicate whether the face had been presented, and if so, in which condition. In this task, recollection was indexed by the proportion of targets that were correctly identified as

old and that were also attributed to the correct encoding condition. In contrast, familiarity was measured by the proportion of targets that were correctly recognized as old, but that the participant could not attribute to the correct encoding condition. The results showed that APOEε4 carriers and non-carriers did not differ on the recollection score, but APOEε4 carriers had a significantly poorer familiarity score. Schoemaker et al. (2016) [5] concluded that individuals at increased risk of developing AD have impaired familiarity. With the caveat that one does not know how many participants will eventually develop AD, as carefully considered by the authors in their discussion, these findings may represent a first step towards supporting the idea of familiarity impairment as an early and specific marker of Alzheimer's disease. However, we would like to suggest that the results do not support (nor contradict) such hypothesis. In this study, recollection and familiarity scores were derived from target faces only and were indexed by the ability to recall (or not) in which condition the face was presented (i.e., source attribution). Critically, familiarity was measured as the absence of recollection. Yet, a portion of recollected faces also probably entailed familiarity for the faces, as recollection and familiarity can co-occur. As a consequence, the contribution of familiarity may have been underestimated [6]. Moreover, even if a participant failed to recollect the encoding condition, s/he may have recalled other details associated with a target face (e.g., personal thoughts, emotional reaction). In other words, the familiarity score may encompass a portion of non-criterial recollection [7]. Finally, the poorer familiarity score in APOEε4 carriers may actually reflect fewer instances of failed recollection. Indeed, when considering the proportion of recognized targets (i.e., hits) that were accompanied by incorrect source attribution (from the means in Table 3 [5]), it appears that failure to retrieve the source occurred for about 53% of the hits in APOEε4 carriers versus around 61% in non-carriers. So, if this difference is significant, the poorer familiarity score in APOEε4

carriers may actually mean that, when correctly recognizing the faces, they retrieved the source more often.

Additional studies aiming at testing the hypothesis that familiarity is selectively impaired in the initial stages of AD are warranted as this is a promising avenue for early detection of AD. The strongest piece of evidence in favor of this hypothesis would be the demonstration of a selective deficit of familiarity in a task that provides a pure measure of this memory function in participants who are shown to have incipient AD, i.e. cognitively healthy individuals who are positive on biomarkers of AD [8] and show cognitive decline in longitudinal assessments.

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References

- [1] M. Didic, E.J. Barbeau, O. Felician, E. Tramon, E. Guedj, M. Poncet, et al, Which memory system is impaired first in Alzheimer's disease? *J Alzheimers Dis.* 2011;27:11-22.
- [2] B. Bowles, C. Crupi, S.M. Mirsattari, S.E. Pigott, A.G. Parrent, J.C. Pruessner, et al, Impaired familiarity with preserved recollection after anterior temporal-lobe resection that spares the hippocampus. *Proc Natl Acad Sci U S A.* 2007;104:16382-7.
- [3] J.D. Koen, A.P. Yonelinas, The effects of healthy aging, amnesic mild cognitive impairment, and Alzheimer's disease on recollection and familiarity: a meta-analytic review. *Neuropsychol Rev.* 2014;24:332-54.
- [4] D. Schoemaker, S. Gauthier, J.C. Pruessner, Recollection and familiarity in aging individuals with mild cognitive impairment and Alzheimer's disease: a literature review. *Neuropsychol Rev.* 2014;24:313-31.
- [5] D. Schoemaker, J. Poirier, S. Escobar, S. Gauthier, J. Pruessner, Selective familiarity deficits in otherwise cognitively intact aging individuals with genetic risk for Alzheimer's disease. *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring.* 2016;2:132-9.
- [6] L.L. Jacoby, A.P. Yonelinas, J.M. Jennings, The relation between conscious and unconscious (automatic) influences : A declaration of independence, in: J.D. Cohen, J.W. Schooler (Eds.). *Scientific approaches to consciousness.* Mahwah, NJ: Lawrence Erlbaum Associates; 1997, p. 13-47.
- [7] A.P. Yonelinas, L.L. Jacoby, Noncriterial recollection : Familiarity as automatic, irrelevant recollection. *Conscious Cogn.* 1996;5:131-41.

[8] R.A. Sperling, P.S. Aisen, L.A. Beckett, D.A. Bennett, S. Craft, A.M. Fagan, 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.