Reviewer's report

Title: Reduced hippocampal activation during episodic encoding in middle-aged individuals at genetic risk for Alzheimer's Disease: a cross-sectional study

Version: 3 Date: 29 August 2005

Reviewer: Lars Nyberg

Reviewer's report:

General

The revised version of this paper reads very well. The authors have addressed the comments I raised in the first round of reviews. I found their addition of whole-brain data very interesting.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The only major comment I have has to do with the VBM findings. The fact that they chose to include such data to rule out volume artefacts in the interpretation of fMRI data is excellent, and the finding of no between-group differences in hippocampal volume makes the interpretation of functional data more straightforward. At the same time, on p 3 of the Introduction, the authors note that many previous studies have observed reduced hippocampal volume in cognitively intact e4 carriers, and they back up this by making references to 8 previous studies (+ one exception). I think the authors in their Discussion (p. 14) should comment on the relation between their findings on hippocampal volume and prior findings. For example, similar to their discussion of discrepancies between functional studies, it may be that the relatively young age of the present sample vs those included in other studies could have played a role.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

In the Abstract, it may be informative to mention the novel/familiar contrast

P 17: the authors make reference to the novel/familiar *recognition* paradigm. At the same time, on p 7 (end elsewhere) they make reference to "encoding". I think this can be confusing to readers and could be clarified.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable
Statistical review: No

Declaration of competing interests:

Non-financial competing interest: In my lab we are doing similar studies (although I do not view this as being in competition with this work I wanted to mention it).