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: 1 Date: 28 June 2005

Reviewer: Matthias Riepe

Reviewer's report:

General

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

The manuscript by Trivedi et al. address important issues for understanding of memory processes and imaging thereof with fMRI. However, clarification and additional analyses will be needed.

1. In the introduction it is argued that E4-carriers show earlier age-related episodic memory decline than non-carriers. This finding, however, is not reproduced in the study. This should be discussed.

2. The literature on fMRI in episodic memory is not sufficiently quoted, e.g. the works by Cabeza et al. and Gron et al.

3. The numbers of patients that actually entered the analysis should be given for each group on page 5. Are the data in table 1 of all individuals or of those, of whom the imaging data were analyzed? It seems that the gender ratio should be different, was chi-square testing used to look for differences? Since gender-specificity of E4-impact on neuronal recruitment is suggested by the study, Table 1 should be extended so that the performance of males and females in the E3/E3 and E3/E4 groups can be seen, individually.

4. Given the large range of age, this factor should be used as a covariate in the imaging analysis.

5. Given the significant difference in the Trail B and that what is known about frontal cortex involvement in successful encoding it would be nice to see a whole brain analysis.

6. Recent literature by Rombouts et al. indicates that not the height of the bold response may be different in controls and AD but the timing. The authors need to discuss this in light of the rather short intervals at which the pictures were presented.

7. To be more sure about whether it is episodic memory, indeed, that is assessed by the fMRI task it would be helpful to see a correlation with the most established measures of encoding from the RAVLT task.

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)

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:

I declare that I have no competing interests.