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: 16 August 2005

Reviewer: Mark W Bondi

Reviewer’s report:

Discretionary Revisions (which the author can choose to ignore)

This is a re-submission of an excellent manuscript that promises to contribute important findings to the neurobiological substrates of episodic memory encoding in middle-aged adults at increased risk for the development of Alzheimer’s disease (AD). Since little is known concerning the brain activation patterns in at-risk groups on susceptible cognitive functions prior to dementia onset, the importance of this study is clear. In short, this reviewer appreciated the authors’ very careful attention to the previous review team’s concerns and the subsequent changes made to this revised manuscript. I have essentially only three minor comments to add for the authors’ discretionary consideration.

First, the authors opine that the evidence for reduced MTL volume in APOE e4 carriers far outweighs the evidence against this finding, and insert 8 references thought to be in accord with this position, although one reference contrary to this position is also provided (given in the prior review). Without belaboring this minor point too much, many of these 8 studies are ambiguous in regards to e4 effects on hippocampal volume. For example, Reiman et al.’s 1998 study reported no significant differences on hippocampal volumes between APOE groups (only nominally smaller volumes), den Heijer et al.’s 2002 failed to equate APOE groups on cognition (e.g., e4 carriers had lower memory scores), Tohgi et al.’s 1997 study measured only one slice of the hippocampus and cognitive compared subjects with only the MMSE, Moffat et al.’s 2000 study showed no initial difference between APOE groups in hippocampal volumes (significant differences were found only when examined longitudinally with subjects who had mild cognitive decline), Lemaitre et al.’s 2005 study is entitled ‘No epsilon 4 effect on hippocampal atrophy’, etc. On the negative side, there are quite a few studies—beyond the Jernigan et al. study referenced in the prior review – that provide evidence against e4 effects on MTL volumes (e.g., Bigler et al., 2002).

Although the particular point may seem trivial, given that it is only one sentence contained in the Introduction under consideration, this reviewer believes that it represents a larger issue within this area of inquiry. If one does not carefully consider the subject characteristics that make up APOE genotypic groups, particularly with respect to carefully characterizing and matching the cognitive status of these individuals, cognitive status and APOE are easily confounded. The result is that any so-called e4 effects on hippocampal volumes (or fMRI-based signal change for that matter) may be due to AD and its early manifestations rather than to the APOE gene per se. In our 1999 study, Bondi et al. showed that APOE group differences on episodic memory (CVLT) disappeared when individuals who later developed AD were removed from both APOE groups. The authors’ own VBM-based analyses failed to demonstrate any differential atrophy in the MTL ROIs by APOE genotype. In all, it seems to be a premature position to conclude “structural MRI studies have found reduced hippocampal volume in cognitively normal e4 carriers.” Moreover, it seems superfluous to the study at hand.
Second, there is still some ambiguity regarding the results reported by hemisphere. For example, the authors choose only to report (and depict in Fig. 2 and Table 2) signal change in the right hippocampus. What happened to the results with the left hippocampus? In contrast, the authors show only the scatterplots between RAVLT and MTL activation in the left hippocampus and amygdala. What happened to the right hippocampus, MTL, amygdala for these analyses? For completeness, reporting the results of both left and right ROIs and scatterplots would greatly facilitate the reader’s inspection of the findings, regardless of whether or not some of these findings attained statistical significance.

Finally, a third study was recently published by B. C. Dickerson et al., 2005, Neurology, using an activation task that had an episodic encoding component (face-name associative encoding) and should probably be added to the discussion of the two other studies referenced in the Discussion section. Importantly, like the Bookheimer et al. and Bondi et al. studies, it too demonstrates increased hippocampal activation among e4 carriers, contrasting with the present manuscript’s main finding.

In all, this reviewer appreciated the careful attention and thoughtful responses to each of the reviewer’s concerns, and the revised manuscript incorporates many changes based on the review team’s recommendations. In addition, this reviewer appreciated the expansion of the Discussion section and possible reasons for discrepancies with the few prior studies in this area. Further work comparing and contrasting fMRI-based findings of episodic encoding in at-risk groups will continue to be an important area of study in need of careful investigation.

**What next?:** Accept after discretionary revisions

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** No