Author's response to reviews

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

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Author's response to reviews: see over
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Dear Editor, BMC Neurology

We appreciate the insight and suggestions provided from the comments to our revised manuscript by the 2 reviewers. We have incorporated their comments into the text of the manuscript and we feel that these changes have significantly strengthened the manuscript. We are enclosing a resubmission of the manuscript. In the following pages we have itemized each reviewers comments and concerns into specific points and we have presented our response below each comment. We have also included the page number on which these changes can be found in the body of the manuscript, and all changes to the text of the manuscript are presented in red. We thank you for considering this manuscript for publication in BMC Neurology.

Sincerely

Sterling Johnson PhD
Mehul Trivedi PhD

Reviewer 1

Lars Nyberg

Report

Critique: “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.”

Response: This is an important issue that was raised by both reviewers. We have significantly increased the discussion of studies examining regional differences in brain volume between e4 carriers and non-carriers. As was highlighted by the other reviewers, the findings regarding volumetric differences between e4 carriers and non-carriers are far from consistent and may be more pronounced at older age. We have added approximately 1 page of text summarizing these studies to the discussion section (see pg 17-18), and suggest reasons for the discrepant findings.
Critique: In the Abstract, it may be informative to mention the novel/familiar contrast.

Response: We have now revised the following statement in the Methods section of the abstract (see pg 2, lines 8-9). The sentence now reads: The present study examined the effects of APOE genotype on brain activation patterns in the medial temporal lobe (MTL) during an episodic encoding task using a well-characterized novel item versus familiar item contrast in cognitively normal, middle-aged (mean = 54 years) individuals who had at least one parent with AD.

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

Response: We have now clarified this to indicate that the construct we are measuring is encoding and this is operationalized in this study as the response to novel items relative to previously learned items.

Reviewer 2

Mark Bondi

Report

Critique: 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.................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.

Response: We appreciate this comment, which was raised by both reviewers. Based on the helpful comments of this reviewer, we have added a page of manuscript text to the discussion section to describe the literature. We felt this addition was justified because fMRI results could potentially be influenced by the partial-volume effect of atrophy. As the reviewer pointed out, there is not yet an emerging consensus on hippocampal volume and APOE. Our revised manuscript should now reflect this fact more accurately.

Critique: 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
Response: It is not yet clear why the relationship with RAVLT total word recall is in the left hippocampus, while the main effect of genotype is in the right hippocampus. Future studies should help in this regard. Given the early state of the literature, we have taken the reviewer’s advice and have included the results of statistical analyses that were conducted in the right hippocampus ROI using the same coordinate as was reported in the left hippocampus. The results of the analyses did not reveal a significant difference between the groups for the left hippocampus. We have included the data for both right and left hippocampal ROIs in Figure 2 and we have included the statistical analyses in the results section as well (see pg 14). We have also included the results of the fMRI signal change correlation with RAVLT total word recall for both the right and left hippocampal ROIs in the results section (see pg 16). We hope these additions will be helpful to readers and facilitate future research.

Critique: 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.

Response: We have now included the important new study by Dickerson et al. (2005) Neurology. This text, on pg 25-26 of the discussion section, includes a summary of their findings as well as possible reasons why our findings are discrepant.