Reviewer’s report

Title: Comparison of brain connectomes by MRI and genomics and its implication in Alzheimer’s disease

Version: 1 Date: 29 Jul 2019

Reviewer: Ronald Killiany

Reviewer's report:

This is an interesting and potentially important study looking for a link between genetic information and brain structural connectivity as it relates to Alzheimer's disease. It makes good use of the Alzheimer's Disease Neuroimaging Initiative data which is in the public domain. It also relies on robust methods that make use of tools in the public domain increasing the likelihood of reproducibility. There are weakness in this work with have the ability to greatly reduce the impact of this study. In my opinion, the greatest of these is the inability of the authors to replicate the findings they have in the ADNI3 cohort in their replication study using the ADNI2 cohort. While they clearly identify this in the manuscript, the basis for this inability to replication is not well addressed. The ADNI3 & ADNI2 cohorts are highly similar to one another in terms of clinical characteristics. Certainly they are far more similar than had the authors drawn a replication study from a totally separate study such as the Framingham Heart Study. This raises significant concern that what they are describing is simple a unique feature of the ADNI3 cohort rather than a widespread phenomenon. I would encourage the authors to look into this more closely and perhaps base their replication findings on effects sizes that are not dependent on subject numbers rather than on p-values that are dependent on subject numbers. Of somewhat lessor importance, there are likely to be rather significant differences in the ADNI3 and ADNI2 diffusion scans. This does not seem to be discussed at all. Finally, it is hard to discern when reading this document if the findings being presented here are the result of a data-driven approach to answer the underlying question (in which case replication is even more important) or if there were specific hypotheses driving the organization of the analyses.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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I am able to assess the statistics

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