Reviewer’s report

Title: A Combination of 3-D Discrete Wavelet Transform and 3-D Local Binary Pattern for Classification of Mild Cognitive Impairment

Version: 3 Date: 19 Dec 2019

Reviewer: Bernd Taschler

Reviewer's report:

Although the nested cross-validation procedure has now been laid out in greater detail, this does not address my earlier point on "maximum accuracy". Presumably the authors mean the average accuracy (over the outer 10 CV-folds). It does not make much sense to report the maximum accuracy in a cross-validation setting and thus the results section should be changed accordingly.

Furthermore, if the number of selected features (based on FDR) was determined in the inner CV loop, how did the authors deal with the prohibitively large number of features for models 3D-DWT and LBP-3D? A brute force search to determine the optimal number of features seems computationally infeasible. How was the optimal set of features for the outer fold determined (assuming there were differences in which features were selected during the inner CV)?

In the case of MCI-C vs MCI-NC classification, 10-fold CV leads (on average) to the inclusion of 7 or 8 MCI-C and about 11 MCI-NC samples in each test fold. Looking at the numbers in Table 2, the low variability seems somewhat surprising (for example, a standard deviation of only 0.0054 for the sensitivity of the best performing method). With such small test sample sizes, are the classification outcomes really almost identical over all 10 folds? Were the folds stratified to ensure similar numbers for both classes in all test sets?

Overall, after several revisions, the explanation of the validation procedure is not clear and detailed enough for me to state confidently that I would trust the results. Without being able to look at the underlying code, I cannot give a clear recommendation for publication. Since the code is not available, I believe I have to leave it to the discretion of the editor (and have therefore changed my recommendation to "discretionary revisions").

Further comments:

- line 190ff: Ref [20] (Chupin 2009) is mentioned as a motivation to use only gray matter because "it has been found that gray matter atrophy is responsible for Mild Cognitive Impairments [20]". This is a rather strong statement and is not fully supported by the findings in [20], which predominantly focuses on segmentation of the hippocampus and, in an application of the proposed method, uses hippocampal volume (not total gray matter) for AD/MCI/CN classification. There are certainly more appropriate references to support the authors' point on the relevance of gray matter for MCI, for example Zhang et al 2012, "Gray matter atrophy patterns
of mild cognitive impairment subtypes" or Apostolova et al 2007, "Three-Dimensional Gray Matter Atrophy Mapping in Mild Cognitive Impairment and Mild Alzheimer Disease".

- It would be useful to have a more detailed interpretation of the updated Figure 2. Why is there a strong bi- or tri-modal structure in the barplots? How should one interpret differences in the normalized number of microstructures between MCI and CN? How to interpret differences between variants of the DWT+LBP model?

- I’d like to stress that it would be best practice to make the code publicly available, for example on github.

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

No

**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?**
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Yes

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