Reviewer Report

Title: A highly predictive signature of cognition and brain atrophy for progression to Alzheimer's dementia

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Reviewer Comments to Author:

This study investigated a machine learning approach to identify high-risk MCI patients using five neuropsychological measures and structural MRI (sMRI). By combining the neuropsychological and sMRI features, the authors identified pMCI patients with 80.4% positive predictive value (PPV) in ADNI1 cohort and 87.8% PPV in ADNI2 cohort. While specificity of the proposed algorithm is high (>%95), sensitivity of the algorithm is fairly low (47.3% for ADNI2). This study addressed an important topic in Alzheimer disease which is to identify high-risk MCI patients. In addition, the manuscript was written well with clear descriptions for the methods and results. However, the novelty of this study is limited. The following comments need to be addressed.
- The emphasis of this study was to achieve a large value for PPV (and specificity) in identification of pMCI patients, but low sensitivity of the proposed algorithm was the cost of this achievement. The authors mentioned that expensive clinical trials can benefit from the proposed algorithm since false positives need to be minimized in this setting. However, this application of the proposed algorithm is arguable in that only a subset of pMCI patients (~50% of pMCI referring to ~50% sensitivity) will be identified by the algorithm and including only these extreme pMCI cases may cause a bias in results of the clinical trials.
- This study has a limited novelty which is to develop an algorithm to provide a high PPV in identification of pMCI patients, in the cost of low sensitivity. There are several studies investigated classification of pMCI and sMCI using neuroimaging (e.g. sMRI and resting-state fMRI) and/or neuropsychological measures (e.g. [Suk et al., 2014, Neuroimage 101, 569-582] and [Hojjati et al., 2018, Comput Biol Med 102, 30-39]. In fact, the authors compared PPV of their algorithm with that of only three previous studies [7-9], and two of these studies were performed by themselves. I recommend to expand this section of discussion by comparing results of the proposed algorithm (i.e. PPV, sensitivity, and specificity) with that of other machine learning studies that used sMRI (or resting-state fMRI) and/or neuropsychological measures as input features.
- Please add a table and summarize results of Figure 2. Please also add accuracy and AUC to this table.
Minor points:
- Line# 132: Please correct "with with"
- Line# 146: I recommend replacing "n subject x n subtype" to "n subject x m subtype (n=377 and m = 7)"
- Line#147: Please spell out VBM.
- Line# 185-186: "three highly predictive signatures (HPS)" in this sentence is confusing. What does the signature mean? Do you mean three models? If not, please define signature here.
- Figures, and in particular Figure 1, have a low quality.

Methods

Are the methods appropriate to the aims of the study, are they well described, and are necessary controls included? Choose an item.

Conclusions

Are the conclusions adequately supported by the data shown? Choose an item.

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Does the manuscript adhere to the journal's guidelines on [minimum standards of reporting?](#) Choose an item.

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Statistics

Are you able to assess all statistics in the manuscript, including the appropriateness of statistical tests used? Choose an item.

Quality of Written English

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None

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