Reviewer's report

Title: Predicting progression of mild cognitive impairment to dementia using neuropsychological data: a supervised learning approach using time windows

Version: 1 Date: 11 Apr 2017

Reviewer: Valeria Kebets

Reviewer's report:

The authors predict MCI conversion to AD using time windows, thus fine-tuning the prediction by adding the time to conversion information. They predict conversion at year 2, 3, 4, and 5, using neuropsychological data as features and testing several classifiers. They compare the predictions obtained with these models with predictions obtained using the First Last Approach (i.e., conversion to AD, no matter the time window). They obtain higher accuracies with their approach, and their accuracies increase with a longer follow-up period.

The rationale for the paper (i.e., the use of time windows to predict MCI conversion to AD) is very interesting and makes a lot of sense in a clinical setting (much more than the First Last Approach as the authors state). However, several methodological points are not clear in the text and could have lead to incorrect results. These points are enumerated below and need to be addressed.

Major points

- It is not clear whether both datasets are used for feature selection, or only the Lisbon dataset; please clarify. In any case, feature selection must be conducted within a cross-validation set, otherwise there is double dipping, and accuracies will be over-estimated, leading to erroneous conclusions.

- Moreover, it is not clear how correlation-based feature selection was applied. Did the authors choose the neuropsychological scores that were more correlated with the conversion to AD? Please clarify.

- The statistical significance was assessed using t-tests and ANOVAs. It is unclear what was the null hypothesis for these tests and whether the tests were applied on AUCs. If the authors want to test whether the predictions obtained with their model were significantly
different from those obtained with the FL approach, then the McNemar's test is more suitable. If the null hypothesis is that the accuracies obtained are significantly higher than chance, then permutation testing would be more suitable.

Minor points:

- The authors state that they want to "obtain a single feature subset to be reported to the clinicians", but the subset of scores then changes for each time window.

- It should be mentioned that specificity and sensitivity also depend on the number of MCIc/MCIInc in each time window - e.g., at year 2, there are many more MCIInc than MCIc, and specificity is higher than sensitivity; at year 3, the numbers are more balanced, and so is the ratio specificity/sensitivity; then, MCIc are more numerous and sensitivity increases over than specificity.

- For comparison purposes between the CV set and validation set, it would be more clear if Figure 6 contained boxplots for AUC, sensitivity and specificity (as in Figure 5) instead of histograms of AUC.

- Many typos, repetitions and grammar mistakes; please correct.
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.

Unable to assess

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?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?
If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal