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: 13 Apr 2017

Reviewer: Isabella Castiglioni

Reviewer's report:

The manuscript is an application of machine learning to the automatic prediction of conversion of MCI to dementia within a given time window. This topic is of extreme interest for the scientific community, because this could return the prediction of conversion within a given period, i.e., within a given number of years from the baseline visit.

However, some major problems must be addressed.

MAJOR COMMENTS

1. NPS: The use of Neuropsychological (NPS) tests (both scores or subscores) as input features for the classifier is somewhat critical, because you use the same NPS tests to assign the labels to the patients. As you may understand, this could affect the classification performance, overestimating these. This point is well explained here: Optimizing Neuropsychological Assessments for Cognitive, Behavioral, and Functional Impairment Classification: A Machine Learning Study (doi: 10.1155/2017/1850909). Please, consider discussing this point and if you cannot solve this, this limitation should be well explained in the manuscript.

2. TIME-WINDOW: it is not clear to me the definition of a time window. For example, the 3-years time window means that you are considering MCI patients that converter within the first three years or between two and three years? If I understood correctly, this should be the first case. This means that when you are classifying, for example, 5-years converter-MCI versus 5-years non-converter-MCI, you are including also those subjects that converted also very early (i.e., within the 1-year time window). This is the reason of the higher accuracy in the 5-years time window. Please, discuss this point. For example, in the 5-years time windows, what is the real "impact" of patients that converted between 4 and 5 years with respect to all the others? Is the classification accuracy really given by the ability to predict conversion 5 years before or this has a low weight? Moreover, I would have tested my classifier on the second approach described above, i.e., considering
MCI patients that convert between two given dates (e.g. between 2 and 3, between 3 and 4, ...).

3. STABLE-MCI INCLUDE CONVERTER-MCI: If I understood correctly, in each group of the time-window approach you label as converter MCI all patients who converted within (for example) 3 years, and you label as stable MCI all patients who did not convert within 3 years from the baseline. By doing this, the stable-MCI group also includes patients that could convert within 4 or 5 years from the baseline, i.e., actually demented patients for which a diagnosis of dementia has not been made yet. Doesn't this introduce some errors in the two groups? Please, discuss this also in the manuscript.

4. FEATURE SUBSETS: "The feature subsets were obtained prior to training, outside the cross-validation chain, given the need to obtain a single feature subset to be reported to the clinicians" - does this mean that the feature subset was obtained using also the training set? This could introduce overfitting to the training set in the CV classification. Please, explain this and remove the classification performance using the CV approach from the abstract. On the other side, you are using an independent validation set, so this should not affect the performance computed on the independent set (which, indeed, results to be lower than CV performance). Moreover, also explain this in the text, and expand the comments of the results on the independent validation set with respect to CV.

OTHER MAJOR COMMENTS

How did you treat the statistically-significative differences in gender and formal education among cMCI and sMCI patients?

"Creating learning examples using time windows": I would not call it "creating" the samples/example (here and in the whole manuscript), because you are only describing your dataset, i.e., the dataset used for classification (features + labels). Moreover, "creating" samples gives the idea that you are making a dataset from zero, maybe "artificially", while your dataset is the one described in the section "Data".

"...where a set classifiers, parameters and preprocessing options are tuned" -> do you mean "...where a set of classifiers, parameters and preprocessing options are tuned"? And what do you mean with "parameters"? And which classifiers? I would explain it in the Methods, rather than in Results.
A lot of the Results section should be moved to the Methods section. For example, all Results from page 10 to 12. Results really begin in subsection "Cross-validation Results: Prognostic using patients from Lisbon".

The full list of considered neuropsychological tests (and which scores or subscores of the tests) should be reported (or recalled) in the Methods section.

MINOR LANGUAGE/WRITING ERRORS (not limited to the ones reported below)

"This process is repeated for each **for each** time window and FL datasets"

"It is composed **by**: 1) the baseline assessment..."

"We use an independent validation set (Figure 2, validating the model) to validate the classification model with the best performance in the CV set" -> "We use an independent validation set (Figure 2, validating the model) to validate the classification model with the subset of features that best performed in the CV set"

"The validation set should be independent from the CV set" -> "The validation set is independent from the CV set"

"The CV set (patients recruited in Lisbon) WAS used to train the model while the validation set (patients recruited in Coimbra) WAS used to validate the model"

SMOTE is used as an acronym without prior definition.

"...based on time windows, which consists IN stratifying the cohort of MCI patients..."

" as it not only predicts whether a MC patient will evolve to dementia" -> MCI
MISSING CITATIONS

In the Introduction, you missed the following papers using Machine learning for predicting MCI:


- Combining multiple approaches for the early diagnosis of Alzheimer's Disease (http://doi.org/10.1016/j.patrec.2016.10.010)

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.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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