Reviewer’s report

Title: Machine Learning Analysis of Motor Evoked Potential Time Series to Predict Disability Progression in Multiple Sclerosis

Version: 3 Date: 04 Jan 2020

Reviewer: Manuel Vázquez-Marrufo

Reviewer's report:

COMMENT: Reviewer
Machine Learning Analysis of Motor Evoked Potential Time Series to Predict Disability Progression in Multiple Sclerosis

After reading the answers from the authors, I still have some concerns about this manuscript:

1. If I have understood well, the main goal of the present study is to improve the possibility of prognostic value using EPTS (specifically MEP) and machine learning.

ANSWER:
This is indeed the main goal. To clarify our main goal, we have rewritten the introduction, and replaced "prognosis" (which is quite general and could mean several things) with the more specific terms "prediction of disability" and "monitoring of disease course". We hope that the new introduction is less vague and more precise.

COMMENT:
Considering that authors refer to "time series" I expect some intervals of points and not only latency or peak to peak measures. Indeed, in the abstract section authors stated "We perform a machine learning analysis of motor EP that uses the whole time series..". Checking the figure 1 it is not marked or defined intervals that are included in the measurement. I would suggest a more clear definition of what is analyzed in this study and included as data for machine learning algorithms.

ANSWER:
It is clear that we did not explain well enough on what part of the time series the feature extraction is done. In contrast to, e.g., visual evoked potentials or somatosensory evoked potentials, we don't need to define intervals: latencies are annotated by specialized nurses. The extra time-series features are extracted from the full signal, so no interval needs to be defined.
To make this more clear, we have added a detailed description of the measuring procedure of the motor evoked potentials in a new section (Section 2.1: Measurement protocol).
We have also expanded on the explanation in Section 2.3, in "feature extraction". In the new version we write (new part in bold):

"Because each EPTS starts with a large peak at the beginning, an uninformative artifact of the electrophysiological stimulation, the first 70 samples of each EPTS are discarded. A diverse and large set of time series features is extracted from the rest of the EPTS (1850 samples) with the HCTSA package, which automatically calculates around 7700 features from different TS analysis methodologies."
Comments from the reviewer (NEW):

I (still) don’t get a clear idea about when the calculation is performed. When authors referred to "1850 samples", what does it mean, in terms of range of response in the MEP? Because, it is probably a huge task to define this interval for each subject, at least it could be defined as a range in the time window where extraction was performed.

Another concern reading the 2.1 section is about that some subjects showed more than one measure, so the calculations were not weighted between subjects. What’s the reason of this procedure?

COMMENT:
2. About noise, this point is highly relevant. The main concern is if authors have used discrete points of measurement (latency or amplitude of peaks) or collection of data in a specific interval. In the second case, noise could be determinant for the results of the application of any algorithm. Signal-noise ratio is one measurement that can help to value the cleanness of the MEPs. Another possibility is to present a grand average of MEP from all subjects just to see the baseline and the MEP wave compared to that.

ANSWER:
Since this was not clear in the manuscript, we have further clarified in the new version that there is no collection of data in a specific interval: we use the full time series to extract features (see previous answer).
Regarding the impact of noise on the features: the machine learning algorithm should be able to deal with the noise, since this is how the MEP are measured in routine clinical follow-up.

Reviewer Comment (NEW):
If the full time series are used, are you also including time before the execution of the response (as a baseline)? And, if authors stated the following: "Because each EPTS starts with a large peak at the beginning, an uninformative artifact of the electro-physiological stimulation, the first 70 samples of each EPTS are discarded." When it is supposed that the extraction starts? The problem to understand all this procedure is that, at least for me, I could not replicate this study because no indications of latencies or peak to peak measurements have been made.

COMMENT:
In any case, specific details of the recording are also missed, for instance, system employed for the study, digitizing rate, time interval used, and so on.

ANSWER:
Specific details have been included in the new section 2.1: measurement protocol.

Reviewer comment (NEW):
The requested information has not been included. I strongly suggest to the authors that take a specific article about ERPs and the usual data included on it (for instance, Coppola G1, Currà A, Di Lorenzo C, Parisi V, Gorini M, Sava SL, Schoenen J, Pierelli F. Abnormal cortical responses to somatosensory stimulation in medication-overuse headache. BMC Neurol. 2010 Dec 30;10:126. doi: 10.1186/1471-
COMMENT:
3. Lastly, I still found the discussion and conclusions far away to be directly applied in the neurology field. As an example, figures that probably are representing diverse results of the algorithms, they do not help in my opinion to understand the potential application in the MS prognostics. My recommendation to the authors is to make a special effort to explain in a more clear way the benefits of their methods for the neurologist.

ANSWER:
The introduction has been rewritten, to make it shorter and more to the point, and to make the relevance to the prediction of disability progression in MS more clear. We hope that the last part in the discussion also shows the potential benefits for neurologists using EP in clinical practice. We made a small change in the conclusion section, to highlight the usefulness for more certainty about the disease evolution, which is relevant for patients.

Reviewer Comment (NEW):
The goal of the study is quite interesting, however, in my opinion, the manuscript is still not clear enough in its contributions to the neurology field.

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

Unable to assess

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 recommend additional statistical review

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Please indicate the quality of language in the manuscript:

Acceptable
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