Author’s response to reviews

Title: A semi-automated measuring system of brain diffusion and perfusion magnetic resonance imaging abnormalities in patients with multiple sclerosis based on the integration of coregistration and tissue segmentation procedures

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Author’s response to reviews:

We are grateful to the Reviewers for their interest regarding our paper, for their accurate annotations and for their helpful comments. Accordingly, we took into account the suggestions of the Reviewers as follows:

In reply to Reviewer #1:

1) Page 3 Line 12 to 22. This sentence contains the main aim of the study, but it is encapsulated in a big paragraph. It would be better to provide a clear explanation, separated from other information, on why it is important to clarify "the actual significance of DWI and PWI abnormalities in MS" and what does this mean for research and clinical practice. Apart from the epidemiological studies, it would be much more worth to highlight clinical relevance and its impact on general health policies.

As suggested by the Reviewer, this segment of the “Background” Section was in part re-written to better elucidate the potential clinical relevance of DWI and PWI changes. However, it is important to underscore that none of the tools included in our Suite and presented in this paper is intended for clinical usage since they represent at this moment only research packages. This aspect was then stressed at the end of the Abstract and throughout the manuscript.
2) Secondly, the rest of the paragraph suffers from some confusion-everything is correct but should be organized better to lead the reader.

As requested by the Reviewer, this segment of the “Background” Section was in part re-organized to make it more readable.

3) Page 3 Line 44 and below: why the chosen approach should be the one indicated by the Authors? It would be helpful if the Authors clearly explain the benefits over other kinds of approach.

As suggested by the Reviewer, an explanation about the choice of the software programs utilized in our Suite was incorporated in the text, at the end of the “Background” Section. Briefly, in absence of a standard method, we chose tools commonly used in the MS literature as well as by our own group. Three related new references were added in the appropriate list.

4) Page 6 LINE 26: "independent form scanner" this appears to be a big deal, obtaining images that do not suffer from changing the equipment - it is of noteworthy relevance even for research. Could the Authors be more detailed on this? Because I have the impression that this sentence might be misleading.

We agree with the Reviewer that this sentence could be misinterpreted. In fact, data format obtained by the reorganization of MRI data is different from data format provided by the various scanners, but does not imply any modifications in information content. Thus, the corresponding sentence reported in the “Pre-processing” paragraph of the “DPP Suite and modules” Section was rephrased to better clarify this issue.

5) Here and there in the manuscript the Authors state that they evaluated the suite on patients (selected from a population) but there are no information concerning this sample - at some point they state "single patient / 5 patients" but there are no other details. It would be really important however to know the clinical features of patients that have been selected to test this suite, as different features could led to differences in brain abnormalities (ie. More severe patients easier to identify). Further, the number of patients on which the suite has been tested is also relevant as variability could affect the entire process starting from the part in which the lesions are mapped into ROIs.

As requested by the Reviewer, detailed information about the five patients used in the “Software Metrics” Section was added in the specific paragraph.

6) One would have expected a study in which the suite is used by different experimenters/clinicians on the same patients and the results are compared to find out whether there are differences related to the individual using the suite - they Authors themselves state that they aim at reducing errors due to operators. As this part of analysis is
missing and there are no control studies / inter-rater studies or other types of statistical procedure to verify reliability etc. it is not possible to know whether this suite is really reliable. I appreciate the Authors use well known modules but as they themselves state this is a semi-automated procedure, so such controls are needed.

We agree with the Reviewer that it is crucial to evaluate whether data coming from the Suite proposed in our study are reproducible. Therefore, a Section entitled “Reproducibility of results”, including new findings which focus on this topic were added in the text before the “Conclusions” Section along with two new tables (Table 2 and 3) and two additional references. We chose to compare the analysis of lesion number and ADC, CBF, CBV and MTT values performed by two different readers in the four focal lesion classes from a group of MS patients. This approach can be considered indicative of the Suite performance since it represents one the most important output of our system. Demographic and clinical details were provided for this patient population and the results obtained were appropriately discussed in the text. In addition, the first reader was added in the list of author.

7) Ms lesions and other brain areas” - but MS lesions are not a brain area. This sentence should be clarified.

We agree with the Reviewer that this sentence could be misleading. Therefore, it was re-written to allow the reader a better comprehension.

8) The machine used seems quite powerful - did the Authors check if with a different equipment the suite still works? Otherwise it should be clearly stated.

The DPP Suite was designed to incorporate all needed software in a Linux virtual machine aiming at maximum portability. During its development the Suite was tested on different equipment, including desktop computers, notebooks and servers, with a broad range of performance levels. The virtual machine was also ported from vmware to native Linux virtual platform kvm. Therefore, as requested by the Reviewer, a short sentence reporting these operational characteristics were added at the end of the “Software Metrics” Section.

In reply to Reviewer #3:

1) The presented software platform is a combination of existing Matlab toolboxes from other researchers, and thus there is no novelty in the algorithms and processes used in the proposed software platform and thus the contributions purely lie in the integration and choice of these toolboxes into a coherent pipeline for measuring brain diffusion and perfusion magnetic resonance imaging abnormalities in patients with multiple sclerosis. However, the choices of particular toolboxes for each step are not well explained or justified, which makes it difficult
for the reader to understand why these particular toolboxes are chosen compared to all the other ones that are available. The authors need to justify clearly why each toolbox is chosen.

We agree with the Reviewer that the main aim of our study is to provide an integrated analysis process for measuring brain DWI and PWI abnormalities in patients with multiple sclerosis. On the other hand, as reported in our reply to point 3 of the Reviewer #1 and at the end of the “Background” Section, standardized algorithms for the procedures involved with co-registration and tissue/lesion segmentation are currently lacking. Indeed, there are a number of comparative studies that have aimed at addressing these points. Even in this regard, the results are often conflicting and may in part be due to differences in pre-processing steps and characteristics of the enrolled subjects. However, it should also be noted that all of the tools that we have incorporated into our suite are widely used in the MS literature. Our proposed suite aims to standardize as much as possible the various steps in the analysis such that results will be more reproducible.

2) The authors need to provide a much more comprehensive explanation and description on the algorithms used by the different toolboxes, so that the reader understands how they work and their strengths and weaknesses.

As reported in the previous answer, this has been the focus of a number of studies in the literature. The aim of our study was not to highlight the particular strengths or weaknesses of the individual components, but rather to provide a description of a modular framework to facilitate the analysis of multi-modal imaging data. As such, we explained in the manuscript how the different components of the external software programs are combined to implement the complete DPP pipeline. However, in our opinion, a complete description of every single algorithm used by different software is beyond the scope of the present work. In addition, the operational/algorithmic details of the individual tools can be obtained from the appropriate references and websites indicated in the text.

3) The experimental evaluation of the software platform is not well defined and very high level without proper details on procedure (e.g., number of patients tested, how many radiologists, what are their experience levels, etc.)

As reported in our reply to point 6 of the Reviewer #1, all this information was provided in the new Section entitled “Reproducibility of results” included in the text before the “Conclusions” Section and in the relative Tables 2 and 3.

4) Also, no ethics approval information is provided so it is hard to judge whether the experiments have been approved.

As requested by the Reviewer, this information was provided at the end of the new Section entitled “Reproducibility of results” included in the text before the “Conclusions” Section.
5) Further, there is no control method to compare their software platform against so the reader does not know whether the time improvement using the proposed software platform is significant.

We agree with the Reviewer that a comparison between different software platforms describing the potential time improvement obtained with our Suite could be interesting. However, in our opinion, this advantage should be intuitive since the integration process of the Suite implies a decrease in analysis complexity and, as a consequence, in time-consuming with respect to the classical approach usually performed in which the different components of the Suite are used separately. In this regard, it is important to note that DPP suite calculates for each patient about 100 values + 6 values for every lesion which are typically the result of a complex and multi-step image processing. Although this point was clearly presented in the “Definition and general description” paragraph of “The DPP Suite and modules” Section, we decided to further highlighted it in the “Conclusions” Section by adding a short new sentence.