Author's response to reviews

Title: Reproducibility of brain metabolite concentration measurements in lesion free white matter at 1.5 T

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Author's response to reviews: see over
Dear editors,

we would like to submit the revision of the manuscript with the title:

Reproducibility of brain metabolite concentration measurements in lesion free white matter at 1.5 T

to “Biomedical imaging Online”.

We want to thank the reviewers for their valuable hints and comments. Hopefully we have addressed all topics of the reviewers except the English language. The manuscript was and is checked by a native North American (Canadian) native English speaker. But it may be, that the underlying “German English” can be seen in the manuscript also after the check. All other topics should be addressed. We cite some basic spectroscopic papers in the introduction as well as we cite some manuscripts about reproducibility and variability of metabolite concentrations inside the brain. Also we clarify, that we do not measure relative or absolute concentrations. Instead for the reproducibility check only the amplitude of the metabolite signal in the time domain is evaluated. The reason for using only this amplitude and additionally the relative concentrations referenced to creatine for the protocols with the best reproducibility are described in Material and Method and also mentioned in the Discussion section. Former table 4 was replaced by a decision flow chart (figure 4), which shows the path towards more and more reproducible protocols.

We hope to have addressed all relevant topics of the referees.

Yours sincerely,

Martin Busch

Attached the comments for the reviewer
Reviewer’s report 1
Title: Reproducibility of brain metabolite concentration measurements in lesion free white matter at 1.5 T
Version: 3Date: 8 May 2015
Reviewer: Chunxia Li
Reviewer’s report:
Reviewers’ comments:
This study investigated an important question related in vivo MR spectroscopy post processing: reproducibility since a lot of detailed work has not to be verified and still controversial. Authors address an important question; however, I have some concerns about the presentation and the interpretation of their measures.
General comments:
1. Concerns about the readability
The manuscript is still hard to follow though authors already tried their best to explain in detail such as using so many tables and figures to address and listed questions and answer them one by one. I strongly recommend authors:

1) to pay more attention the connection words between narration and tables and figures to make it to be understood and followed easily.
   We add some references to tables and figures

2) A simple flowchart might be very helped to explain how the equation works to compare if paired spectra get more reproducibility or not.
   We insert a flow chart as Figure 4 instead of table 4.
3) Reorganize the 7 questions and answers and related tables and figures to reduce repeated narration and make answers clear.
We did that with respect to the inserted flow chart figure 4.

2. Lack of sufficient reference citation.
In the introduction and discussion sections, authors should back up their summary or discussion with sufficient reference citations. Authors should check thoroughly to make sure reference is adequately cited.
We add some basic spectroscopic citations in the introduction and publications about reproducibility and variability in the discussion.

3. Table and table information errors.
All the top and bottom line of tables are missing. Some information in tables is not label clearly. Please refer some paper to make correct table and make sure all information in each table sufficiently and separately interpreted.
We give every table at the top a summarizing title followed in some cases by a detailed legend.

Specific comments:
Abstract:
Line 46: (minimal mean chi2) can be deleted.
We delete that.

Methods:
Line 167: “Six saturation pulses were positioned along each plane of the cube (figure 1) for outer volume suppression.” I just find 4 saturation pulses, please explain, or label or replace the figure.
We clarify this by numbering the saturation pulses marked as bars in figure 1 from 1 to 6

Line 304: “no 5” should be “No 5”?
We correct this.

Line 308: (table 6) plus figure. 3?
Figure 3B

Discussion:
Line 380: “The minimal signal to noise ratio for the amplitude of a metabolite was fixed consistently to eight.” What does this sentence mean? Why is eight?
We insert a hint to material and method. The value eight is the default value of the software metabolite report and was never changed. The value 8 means a metabolite has to have a signal to noise ratio of at least eight. Otherwise the metabolite is not respected within the fit. See explanation in material and method.

We explained in little more detail, that for pure reproducibility evaluation neither absolute nor relative concentrations are necessary. The best reproducibility can be evaluated by looking at the amplitude of a metabolite in time domain only.
Additionally we check the two best protocols as relative metabolite concentrations with reference to the creatine CH3 group.
“Figure 1”. please show the volume of voxel selected for for spectroscopy.
We mark it as VOI in figure 1A to figure 1C

“Figure 2”. Please give a detailed description of model metabolites.
We add a structure formula of the main metabolites in figure 2 and add a table in the legend of figure 2 with the TE values, the chemical shift of the main lines as well as the properties or function of the metabolite.

“Figure 3”. lipid information is interesting, which has been reported as biomarkers for differentiation between brain tumors and healthy tissue. Please tell how many cases you found these macromolecular components.
We mention that in most cases we did not found any or only one lipid line see figure 3B, which is, if present, often dominated by macromolecules. Because the test subjects are all healthy young people this result is as expected.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being Published
The manuscript was and is checked by a native North American (Canadian) native English speaker. But it may be, that the underlying “German English” can be seen in the manuscript also after the check.
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests.