Author's response to reviews

Title: Valid and efficient manual estimates of intracranial volume from magnetic resonance images

Authors:

Niklas Klasson (niklas.klasson@neuro.gu.se)
Erik Olsson (erik.olsson@neuro.gu.se)
Mats Rudemo (rudemo@chalmers.se)
Carl Eckerström (carl.eckerstrom@neuro.gu.se)
Helge Malmgren (helge.malmgren@filosofi.gu.se)
Anders Wallin (anders.wallin@neuro.gu.se)

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Author's response to reviews: see over
Dear editor and reviewers,

We are glad that both reviewers found most of our previous changes to the manuscript acceptable, and hope that this revision will be fully acceptable. Besides changes done in response to the comments of reviewer 1, a few stylistic changes and some minor additions referring to the most recent literature have also been included. Below is our response to the comments of reviewer 1.

Best regards,

Niklas Klasson

**Response to reviewer 1:**

1. In section 4 paragraph a) was added:

   a) The methods and settings used for preprocessing the image data in the present study might have been suboptimal. Specifically, the reformatting of the image data was done by a linear interpolation when other interpolation methods would arguably have been better [24]. However, the error introduced by the linear interpolation is likely negligible because of the large size of the ICVs.

2. It is true that Pearson’s correlation is not optimal when evaluating the quality of the intracranial volume estimates. However, we still do not think that an overlap analysis is essential in the manuscript to thoroughly evaluate the validity of the estimates. The kind of examples given by the reviewer to explain the problem with Pearson’s correlation would have clear effects on the intraclass correlation with absolute agreement as well as on the percentage errors. This can for example be seen for the linear interpolation in Figure 3. While the linear interpolation generally had quite good Pearson’s correlation it tended to underestimate the intracranial volume (seen by the percentage error), which had a negative effect on the intraclass correlation.

Still we added the Jaccard index to the manuscript with regard to the extended possibility to compare the current result with other studies. The following changes were done:

In the first paragraph of section 2.5, sentence a) was changed to b):
a) For each setting, Pearson’s linear correlation coefficients and intra-class correlation coefficients (ICC) were calculated for each of the 2000 combinations in relation to the ICV segmentations.

b) For each setting, Jaccard index values, Pearson’s linear correlation coefficients, and intra-class correlation coefficients (ICC) were calculated for each of the 2000 combinations in relation to the ICV segmentations.

In the last paragraph of section 2.5, sentence d) was changed to e):

d) ICC values were calculated using the external MATLAB function ICC written by Arash Salarian that is available online at the MATLAB file exchange homepage [16].

e) ICC values were calculated using the external MATLAB function ICC written by Arash Salarian that is available online at the MATLAB file exchange homepage [16], and Jaccard index values by the function $\frac{\sum_{n=1}^{62} \min(x_n, y_n)}{\sum_{n=1}^{62} \max(x_n, y_n)}$ [17], where $x$ is a vector containing the 62 actual ICVs and $y$ a vector containing the given combination of corresponding ICV estimates.

In the first paragraph of section 3, the sentences in f) was changed to the sentences in g):

f) Figure 3 shows the ICCs, Pearson’s correlations and percentage errors of the ICV estimates compared to the ICV segmentations. Except for some oscillations, particularly visible for piecewise constant interpolation, the ICCs and Pearson’s correlations generally decreased and the percentage errors increased with increased linear spacing.

g) Figure 3 shows the ICCs, Pearson’s correlations, Jaccard index values, and percentage errors of the ICV estimates compared to the ICV segmentations. Except for some oscillations, particularly visible for piecewise constant interpolation, the ICCs, Pearson’s correlations, and Jaccard index values generally decreased and the percentage errors increased with increased linear spacing.

In the sixth paragraph of section 4, the sentences in h) was changed to the sentences i):

h) While the piecewise linear interpolation increasingly underestimated the volumes, resulting in low ICC, the Pearson’s correlation remained high. This was true regardless of ICA orientation. The cubic spline interpolation on the other hand resulted in improvements of ICC, Pearson’s correlation and absolute percentage error (Figure 4), but only for sagittal and coronal ICAs.

i) While the piecewise linear interpolation increasingly underestimated the volumes, resulting in low ICC and Jaccard index, the Pearson’s correlation remained high. This was true regardless of ICA orientation. The cubic spline interpolation on the other hand resulted in improvements of ICC, Jaccard index, Pearson’s correlation and absolute percentage error (Figure 4), but only for sagittal and coronal ICAs.

Further, changes were done in Figure 3 and its legend to include the Jaccard index analyses.
3. In the last paragraph of section 3, sentence a) was changed to b):

a) Further, the distributions of the ICVs seem to be the same regardless of group belonging ($p_{all} = 0.977$, $p_{females} = 0.458$, $p_{males} = 0.672$), while a difference in mean ICV could be seen by gender ($p < 0.001$).

b) Further, the distributions of the ICVs did not differ due to group belonging ($p_{all} = 0.977$, $p_{females} = 0.458$, $p_{males} = 0.672$), while a difference in mean ICV could be seen by gender ($p < 0.001$) where the females had a mean ICV of 1416955 mm$^3$ (standard deviation: 91678 mm$^3$) and the males a mean ICV of 1658268 mm$^3$ (standard deviation: 115535 mm$^3$).