Reviewer's report

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

Version: 4 Date: 24 October 2014

Reviewer: Alexander Hammers

Reviewer's report:

I thank the authors for their consideration of most of my and the other reviewer's comments. Two points remain about which I feel strongly enough to keep them in the compulsory revisions section.

“Major compulsory revisions”

1. Section 2.3: The interpolation method is now given; linear interpolation was used which is suboptimal for MRI. This is an important detail as interpolation can have a major influence on more detailed measurements (e.g. Ahsan RL et al. Neuroimage 2007 38:261-270). I think it is highly unlikely this would make much of a difference for large structures like intracranial volume (ICV), but the authors present by far the most detailed paper on ICV determination, and following generations of researchers with a need for determining ICV will likely turn to this paper. It should therefore be added e.g. in the discussion that a suboptimal interpolation method was used during preprocessing, that it is unlikely to matter in the context, but that generally windowed sinc or B-spline interpolations should be used.

2. Section 2.5: Adding measures of overlap is essential for assessing quality. I do not agree with the authors’ explanation that correlations are sufficient. Take the extreme case of \( y=x+1400 \text{ cm}^3 \): the correlation coefficient between \( y \) and \( x \) can be 1, but the ICVs obtained will be double those in the reference method, and ratios will not be comparable between papers. \( y=5x+0 \) would be worse: tight correlation, but a changing relationship between actual and estimated ICV which could potentially lead to diametrically opposing conclusions about the underlying biology between papers using a different methodology.

Measures of overlap, e.g. Jaccard indices, are the best way of providing an impression of the accuracy of the method, and the only way of comparing the authors’ data with other studies using only such measures. In the authors’ case, overlap measures would presumably provide the additional benefit of highlighting a much smaller overlap with ground truth for the piecewise constant interpolation method for larger sampling spacing and would have allowed to highlight this difference between the methods which is not captured by the correlations used.

Prof. Heckemann in your institution is an expert on the issue and could provide scripts for determining overlaps if needed.

3. Intracranial volumes are now shown in the very useful Figure 5. Could the
actual values \( (\text{mm}^3 \pm \text{SD}) \) for men and women be given in the paper or the legend as well? This will be very useful for other groups.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**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 as defined above.

Of course I will benefit from the paper being published, seeing that some of our work is being cited; thanks to open peer review my name will appear and document community contribution which it would not do if I had rejected the paper. My career like everyone else’s partially depends on all these things.