Reviewer's report

Title: Early microstructural white matter changes in patients with HIV: a diffusion tensor imaging study

Version: 1 Date: 5 December 2011

Reviewer: Miriam H. A. Bauer

Reviewer's report:

The paper deals with the question of early detection of white matter changes as predictive value for development of clinical symptoms and changes in treatment of these patients. Therefore, the paper reports on differences in white matter fractional anisotropy in HIV patients with and without mild macroscopic brain lesions, resulting in FA alterations in regions adjacent to observed lesions and corresponding areas in both groups. Furthermore, white matter alterations were correlated with neurocognitive deficits and depression, where patients with evidence of depression showed an increase of FA in defined areas, whereas patients with evidence of HIV-associated neurocognitive disorder showed widespread FA reduction.

Major Compulsory Revisions:
• The control group is age-distribution matched. There are only male patients, but the control group is mixed. There are several papers reporting on the differences in FA-values between man and women (e.g. Menzler et al. 2010, Neuroimage). I would suggest, discussing this “mismatch” somehow and explaining, why there’s no impact on the result. (page 4)
• The “new finding” of similar regions with reduced FA values for patients with and without macroscopic lesions could be discussed in a little more detail (e.g. are there any DTI studies with similar patients or different regions of interest) because of this “interesting” new result in correlation with its possible benefits (page 11)

Minor Essential Revisions:
• The authors clearly motivate the use of diffusion tensor imaging as possible predictive method for development of clinical symptoms and according implications of treatment. The first goal (early detection of white matter alterations) is clearly motivated and stated. The second goal could be stated more precisely also in correlation to the first goal. (page 3-4)
• Data acquisition is only described for diffusion tensor imaging. As also structural MRI was used for including/excluding patients for this study, acquisition parameters for these measurements should be declared somehow (if done for all patients in the same way). At least, the MRI system and field strength should be listed. (page 4)
• In section “Diffusion tensor Imaging”, VBS is used as abbreviation but not
introduced before (page 4)

- SPM is mentioned in section “DTI”, a reference should be inserted and the abbreviation should be introduced (is done later on page 6).
- Results of all ROIs for patients vs. controls are presented, but the ROI “brain stem” is missing in this part for goal 1, FA values are mentioned in table 2 (page 7, top)
- Line 5 after Figure 3: “who were not” should be replaced by “who not” (page 7)
- “FA reduction” instead of “FA reduction increase” in Section 3.2. (page 8).
- A p-value is missing for comparison of HIV patient with neuropsychological evidence for HIV associated neurocognitive disorder and HIV patient without evidence showing a significant widespread FA reduction (page 8)
- “FA reduction” instead of “FA-reduction” for uniformity (page 9, line 8)
- “mean diffusivity” instead of “man diffusivity” (page 9, section 4.1, line 7)
- “employs” instead of “employ” (page 9, section 4.1, line 8)
- The abbreviation MD for mean diffusivity should be introduced (page 9)
- “reach” instead of “reached” (page 9, section 4.2, line 10)
- “HIV patients” instead of “HIV-patients” for uniformity (page 11, section 4.4, line 16)
- In the conclusion lesions and depression are mentioned, but some concluding result according to neurocognitive impairment is missing.
- Table 1: in the legend with “ew” there a mistake in writing “medication”, and some abbreviations should be introduced like “HAART”, “CDC” and “CD4”, maybe also at least a reference for HIV infection classification should be given for values “B3, C2 and so on”. Furthermore there are 3 times “?” and several times “unknown” in this table. Maybe in the Methods part there should be explained why, or which impact this has.
- Figure 1: the left picture should be labeled with “A” the right one with “B” according to figure legend.
- Figure 2: the subimages should be labeled with “1” to “5” according to the figure legend, or within the figure legend insert “(from left to right)”
- Figure 3: in the Figure legend add something like “for all defined ROIs”. Additionally, the same scale for all results would be good.
- Figure 5: in the figure legend, line 2, “9” should be written as “nine” for uniformity

Discretionary Revisions:

- The period of data acquisition should be declared somehow (page 4)
- It would be interesting to give information on the more “liberal” thresholds used for the figures, in relation to the “real” ones. (page 6)
- In the conclusion it could be added something like “DTI detects early microstructural WM alterations in contrast to structural imaging techniques in HIV
patients” to underline its potential power.

**Level of interest:** An article of importance in its field

**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.