FACULTY OF MEDICINE
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Subject: **Opponent's report on habilitation thesis**

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Title of the thesis:	Clinical relevance of brain atrophy measures in multiple sclerosis

To Whom It May Concern,

It was a great pleasure to evaluate Dr. Uher's habilitation thesis. In his thesis, by collecting his own highly cited publications, he evaluated various MRI markers in the care of multiple sclerosis (MS) patients. While brain atrophy is one of the most promising biomarker in MS both in term of predicting long term outcome and evaluating therapeutic efficacy, validation of the marker and the used analytic approaches has a key importance. The excellence of the work lays not only in the correct application of existing analytical approaches, but the analysis software package developed in Prague has a worldwide fame.
The author summarised his results over 90 pages plus more than 250 references. The manuscript starts with a good summary of the literature about MS and about various MRI markers. The aims are clearly stated. In the next eight chapter the author gave a brief description of eight studies. Seven out the eight studies have already been published in international peer-reviewed, high impact journals that also adumbrates the high quality of the work. The acquired data is plentiful, the statistical analysis is appropriate. The figures, presented after each section help well the understanding. The thesis concludes with a general discussion of the results of the studies.
The thesis is well written in clear English, only a few typo can be found here and there that does not interfere with the understandability.
I enjoyed reading this excellent thesis and the following questions and suggestions occurred to me:

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Introduction

- On page 14, the author mentions the reasons behind the clinic-radiological paradox. What might be the cause other than the specific topography?
- In section 1.6, it would have been nice to give an overview of the evolution of diagnostic guidelines.
- Probably in section 1.7 the relative effectivity of the DMDs should have been mentioned, with the relevant pivotal studies.
- At some point it would have been nice to introduce the terms: markers, biomarkers, surrogate markers.

Methods:

- It would have been worth to indicate for the non-Philips users, that the T1-WI/FEE is a gradient echo sequence.
- For the subtraction analysis in BNAC, no normalization was used. This makes the analysis rather difficult, while easy to use approaches are available (eg: Nyul et al., 2000, IEEE Trans Med Imaging). What was the normalization approach in Prague?
- What was the bias field correction approach used for the FLAIR images in BNAC?
- I might have missed it, but I'm not too sure what WB stands for. Is that whole brain? Mind you, I haven't found that in the original paper either.
- What is the learning effect for BICAMS test over annual testing? How the author have dealt with this issue?

Results

- 5.1 Results and discussion: "We suggest that stronger correlations among cross-sectional measures can be explained by lower inter-subject biological variability of longitudinal data." I'm not too sure, how this could happen. I would expect higher correlation for longitudinal measures because of this reason. The lower correlations for the longitudinal measures are more likely stem from the different analytic approaches. As described, ScanView calculates the brain volume change from the two cross-sectional results, based on intensity based segmentation. SIENA on the other hand calculates brain volume change from edge displacement.
- 5.2 Is there a cut-off for differentiating patients with active disease (relapse, new T2/enhancing lesion, EDSS progression, need for change of therapy) and those who are stable?
- 5.3 Could the precision of brain volume change estimation be more precise if scans around relapses are not taken into consideration?

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- 5.5 Is there similar data about other disease modifying drugs?
- 5.6 The predictors in this analysis are correlated. How did the authors dealt with the collinearity problem, which is an issue for regression analysis?
- 5.7 It was shown that cognitive impairment depends heavily on sex, education and clinical status (see Sandi et al., 2017). How did the gender influence the results? Did the authors record education?
- 5.8 Would it be possible to resolve the clinico-radiological paradox, in terms of lesion-symptom mapping in more advanced patients too?

Discussion

- When discussing the relationship between brain atrophy and lesion burden, location of the lesions might also be important (see. Jehna et al., 2015 and Toth et al., 2017)
- What does the author think, what is the power of the investigated MRI measures (lesion burden, atrophy) in comparison to other advanced MRI measures (eg., MTR, DTI, myelin content, various fMRI parameters) or molecular markers (light chain etc)?

These questions and suggestions stand here more of scientific interest and not to reduce the value of this excellent thesis. Altogether, ***the thesis contains new important scientific knowledge. I recommend accepting the habilitation thesis in the present form and, based on this thesis, I recommend granting the degree of Docent (Associate Professor) in Neurology.***

Yours sincerely,

[redacted]

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director

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