Author's response to reviews

Title: Clinical correlates of grey matter pathology in multiple sclerosis.

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Author's response to reviews: see over
Dear editor, Dr. Zivadinov,

Thank you and the reviewers for the revision of and helpful comments on the invited manuscript "Clinical correlates of grey matter pathology in multiple sclerosis" which had been prepared for the special issue "Grey matter pathology in multiple sclerosis". We have addressed the issues raised by the reviewers as follows:

The length of the manuscript has been reduced, particularly that of the Assessing grey matter pathology section. A number of single-reference statements have been omitted.

The Physical disability is now the first sub-section of the Clinical correlation section. It has also been divided into sub-sections.

The statement describing the restless legs syndrome has been corrected.

Table giving an overview of the most relevant works studying relation of grey matter changes to the clinical image of MS has been added.

The cognitive impairment subsection has been expanded and sub-divided.

The heading GM impairment: marker and predictor has been changed to GM as a surrogate marker. This section has now been sub-divided, with a sub-section dedicated to the GM as a marker of treatment efficacy.

The concluding statement has been altered.

We have added the Competing interests and Authors’ contributions sections.

The text has been language-edited.

Below is discussion to some of the points raised by the reviewers:

Reviewer 1:

We agree that the possible reason for more benign clinical course of MS might be the less prominent accumulation of MRI damage. At the same time, both of these factors may result from the more efficient regeneration and compensation. Yet, there are other mechanisms that could play roles here, such as lower level of immune activation or individual differences in the patterns of immune response. Therefore we have modified the statement at the end of the GM reorganisation sub-section to involve these aspects.

We believe that not only specificity but also sensitivity of the disease course prediction might be improved by including the regional GM atrophy among the predictors compared to prediction based on the global markers of brain atrophy only. If so, this is likely to stem from better categorisation of variance (thus diminishing the residual error). In contrast, global brain atrophy introduces higher variance in the prediction models, as a large number of undifferentiated structures and processes is involved (e.g. oedema and its resolution due to therapy, pseudoatrophy, selective impairment of specific structures). For example, we have shown that
change in the corpus callosum is more sensitive marker than the global brain atrophy (this work is reviewed for publication). The same may apply to the association between selected structures and cognitive decline (such as thalamus – see Cognitive impairment, Regional GM changes, paragraph 1).

Reviewer 2:
The aim of this manuscript is to present overview of structural changes of the grey matter in the light of clinical findings in MS, and the information regarding histopathology and the overview of MRI techniques will be addressed in other review articles in the planned issue. Therefore, rather than expanding the sections describing these topics, we have opted for their shortening, as suggested by the editor.

Known associations between global and regional changes and the specific neurological presentations have been given in the Regional GM changes sub-section. Two most common disability scales and their relation to MRI changes have been outlined in the Evaluation of disability sub-section.

All authors have approved the final version of the manuscript.

Best Regards,

Tomas Kalincik and Dana Horakova, first authors