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Dear Editor of IEEE Transactions on Medical Imaging,

We hereby submit the manuscript entitled "Deep 3D Convolutional Encoder Networks with Shortcuts for Multiscale Feature Integration with Application to Multiple Sclerosis Lesion Segmentation" by Tom Brosch and Roger Tam as an original research paper to the special issue on Deep Learning. We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal.

This work is original research that substantially extends our previous conference paper on segmenting multiple sclerosis (MS) lesions in magnetic resonance images (MRIs)[1]. The accurate segmentation of MS lesions is a prerequisite for deriving imaging biomarkers, such as lesion load and lesion count, that have established their importance for assessing disease progression and treatment effect. However, lesions vary greatly in size, shape, intensity and location, which makes their automatic and accurate segmentation challenging. We present a novel segmentation method that can automatically learn features that are robust to the large variability of MS lesions from training data. We have substantially extended our previous method to allow for the automatic learning of features on different scales in order to capture a broader spectrum of MS lesions. To allow for a direct comparison with Lesion-TOADS, an established method for the fully automatic segmentation of MS lesions, we have evaluated our method on a new data set containing pairs of T1-weighted and FLAIR MRIs, which are the image modalities that are required by Lesion-TOADS. Our evaluation shows that our new approach significantly improves lesion segmentation accuracy over Lesions-TOADS. In addition, we show that the extensions to our previous work significantly improve accuracy, especially for large lesions, which are the most challenging type of lesions for our method.

Thank you for your time in processing this manuscript and we look forward to feedback from you and the reviewers.

Yours sincerely,

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[1]Tom Brosch et al.. Deep convolutional encoder networks for multiple sclerosis lesion segmentation. In *A. Frangi et al (eds.): MICCAI 2015, Part III, LNCS vol. 9351*, pages 3–11, Springer, 2015.