for the identification of layer-specific myelin changes in early-affected, late-affected and non-affected body part areas in M1 and to monitor disease spread body-part-wise and layer-wise in subsequent scans. This approach may offer the possibility to detect M1 microstructural changes at a stage before the disease spreads through L2/3 connections to other topographical areas, or to the contralateral hemisphere, but after the disease has spread from L5 to L2/3, and would thus allow testing the model as proposed by McColgan et al.

In summary, when investigating neurodegenerative disease spread in M1, it is of critical importance to consider local microstructural gradients and the inherent differentiation between topographical areas within M1. Their combined investigation at different clinical stages may allow novel pathophysiological insights into disease spread as well as insights into which individual profiles of the local myeloarchitecture and cell architecture relate to slow versus fast disease progression (that is, factors that constitute microstructural resilience).

There is a reply to this letter by McColgan, P., Joubert, J., Tabrizi, S. J. & Rees, G. *Nat. Rev. Neurosci.* https://doi.org/10.1038/s41583-020-00405-9 (2020).

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Competing interests
The authors declare no competing interests.

Reply to 'Topographical layer imaging as a tool to track neurodegenerative disease spread in M1'

Peter McColgan, Julie Joubert, Sarah J. Tabrizi and Geraint Rees

We would like to thank Stefanie Schreiber, Alicia Northall, Miriam Weber, Stefan Vielhaber and Esther Kuehn for their interest in our Review (The human motor cortex microcircuit: insights for neurodegenerative disease. *Nat. Rev. Neurosci.* **21**, 401–415 (2020))[1] and their correspondence (Topographical layer imaging as a tool to track neurodegenerative disease spread in M1. *Nat. Rev. Neurosci*. https://doi.org/10.1038/s41583-020-00404-w (2020))[2]. Their comment adds an important technical point about the directionality of myelin gradients. They highlight a seminal study that demonstrates the somatosensory cortex 3b and motor cortex 4 are not homogeneous, as suggested by Brodmann[3], but can be parcellated into sub-fields with clear boundaries, representing hand and face areas. This is eloquently demonstrated using a functional MRI task to identify hand and face areas and 7T MRI to identify myelin borders between these regions at the individual level[4].

This provides a compelling framework, in which the spread of neurodegenerative disease could not only be tracked across cortical layers but also across body topography, enabling a 3D representation[5]. The authors identify amyotrophic lateral sclerosis (ALS) as disease, which can spread body-part-wise initially across the ipsilateral and then the contralateral hemisphere. Indeed, the latter is in keeping with our model showing loss in neurons in the contralateral hemisphere via the death and axonal dying back of ipsilateral intratelencephalic neurons.

The 3D framework proposed may also be applied to other neurodegenerative diseases that demonstrate selective vulnerability of somatosensory and motor cortices. Idiopathic Parkinson disease, for example, typically has a unilateral onset, initially affecting upper limb and may then progress with lower limb symptoms such as dystonia and eventually affect the contralateral side[6]. Huntington disease can also present with subtle chorea, such as finger flicking in the upper limbs on walking, with more generalized chorea and focal limb dystonia as the disease progresses[7].

While the framework proposed by Schreiber et al. may provide a unique opportunity to generate layer-specific and topography-specific measures of motor cortex structure and function, it is not without challenges. As Schreiber et al. highlight, M1 exhibits a surprisingly high heterogeneity even in healthy individuals. This may pose challenges in quantitatively comparing myelin patterns in patients with neurodegenerative disease, where large participant numbers may be required in order to differentiate between naturally occurring population variations in myelin distribution and disease-related effects.

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Competing interests
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