Radiology

Staying Connected: The Relevance of Motor-specific Transcallosal Fibers

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MRI has a pivotal role in the treatment of patients with multiple sclerosis (MS) in both diagnosis and monitoring (1). Conventional MRI findings such as lesion burden and cerebral atrophy only partially explain the degree of disability within the MS clinical spectrum, a mismatch also referred to as the "clinico-radiological paradox" (2). Before considering the limitations of MRI, it is important to note that disability can be defined and measured in many ways and the widely used Expanded Disability Status Scale (EDSS) relies heavily on locomotor disability and walking.

On the MRI side of the equation, numerous studies leveraging advanced MRI techniques (eg, diffusion MRI or functional MRI) have proposed imaging signatures to help better explain impairment according to a variety of clinical outcomes beyond EDSS, such as cognition and upper limb function. Indeed, delivering clinically useful MRI markers is one of the main challenges of translational neuroimaging and is the object of growing interest (3).

For many tasks, white matter fibers connecting different regions play a crucial role. In addition to important descending tracts, such as the corticospinal tract and intrahemispheric association fibers, and transcallosal fibers subserve more complex processes requiring interhemispheric connections. In patients with MS, many tracts are damaged because of widespread lesional and normal-appearing white matter injury. In particular, the corpus callosum is a site of early MS lesion involvement and callosal atrophy, a common finding in MS.

In this issue of *Radiology*, Cordani et al (4) used a multimodal approach that combined diffusion-based tractography and resting-state functional MRI to investigate the relationship between structural and functional abnormalities of motor-related interhemispheric homotopic connections with both global clinical disability and upper limb motor impairment in a large cohort of 340 patients with MS and 130 healthy control patients. In this cross-sectional retrospective study, the authors focused on connections between specific areas subserving hand function. They performed a tract-based analysis (defined in standard space and warped to the individual patient's anatomy) of diffusion MRI–derived measures of white matter microstructural integrity. Their analysis demonstrated widespread damage in hand-related fibers within the corticospinal tracts of patients with MS, and in transcallosal fibers connecting homologous regions of premotor cortices, supplementary motor areas, and hand-related primary motor cortices.

The authors split the patients with MS into groups according to disability milestones, measured with the EDSS, and specific measures of upper limb motor impairment. They then used a machine learning framework based on random forest classification to select the most informative features derived from MRI and quantify their relative importance for predicting clinical status.

Microstructural damage of the analyzed transcallosal tracts was consistently found to be among the most relevant features for predicting global disability and upper limb motor impairment (accuracy range, 69%–89%; $P < .001$ to .049), beyond established imaging markers of disease severity (eg, normalized brain and gray matter volumes, lesion load). Interestingly, MRI-derived predictions failed to identify patients reaching the highest disability milestone (EDSS $\geq$ 6.0), most likely because no spinal cord metrics were included. However, diffusion-tensor MRI measures had good predictive value for hand function impairment according to two complementary measures of manual dexterity. These results, pointing at a specific MRI-symptom correspondence, have clinical relevance because upper limb

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Conflicts of interest are listed at the end of this article.

See also the article by Cordani et al in this issue.

dysfunction is one of the core deficits affecting patients with MS, greatly impacting quality of life (5).

Contrary to the positive findings with diffusion-tensor MRI, a voxel-mirrored homotopic analysis of resting-state functional MRI data showed that functional connectivity of motor-related areas was not significantly altered in patients with MS, and it did not contribute to explaining the clinical status of the patient. These results confirm that the relationship between structural and functional connectivity is seldom straightforward, given the influence of a variety of confounding factors (6). Interestingly, the authors did observe an inverse relationship with disease stage, with increased homotopic functional connectivity of the premotor cortex in more disabled patients probably reflecting disruption of the transcallosal inhibitory mechanism.

This study corroborates and expands the current knowledge regarding the clinical relevance of microstructural damage of transcallosal fibers in patients with MS. Classically considered as a preferential site for demyelinating lesion location in MS (7), the corpus callosum is the largest set of commissural fibers in the brain. Its structural damage has been associated with different facets of MS-related disability, from motor impairment to cognitive deterioration (8,9). From a motor function perspective, the results by Cordani et al (4) corroborate our current understanding of motor control as a bilateral process, even for unidextrous movements, critically depending on transcallosal white matter tracts connecting homologous motor-related areas (10).

Whereas the results by Cordani et al (4) provide valuable insights into the pathophysiologic causes of motor impairment in patients with MS, the question remains of whether the proposed diffusion MRI–derived metrics may serve as useful imaging markers in clinical practice. Diffusion-tensor MRI acquisition parameters may vary considerably, and details of the postprocessing will affect the obtained values further. The proposed analysis pipeline requires matching of templates containing the healthy control tracts, which are not publicly available. In clinical practice, more classic measures of corpus callosum involvement, such as callosal atrophy, may be more readily available.

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