# New imaging language skills required in MS

Maria Pia Sormani, PhD
Nikos Evangelou, FRCP, DPhil

Correspondence to Dr. Sormani: mariapia.sormani@unige.it

*Neurology*® 2015;85:1096–1097

One of the key problems in clinical research involving persons with multiple sclerosis (MS) is the moderate correlation between widely used MRI metrics of tissue damage, such as lesion load and brain volume loss, and clinical measures of disability, such as the Expanded Disability Status Scale (EDSS).[1]

Pardini et al.[2] tried to tackle this issue by combining multiparameter imaging with graph theory (GT), a mathematical approach increasingly used in neuroscience to quantify the integrity of brain networks. GT takes into account which components of a network are connected between each other and the strength of these connections. This potentially leads to the quantification of network-wide properties, such as network efficiency, which represents the ability of a network to exchange information among its components.[3]

In this study, the authors used a technique called constrained spherical deconvolution tractography[4] to create a mask of the average trajectory of the white matter tracts included in the motor network in a group of 22 healthy controls. They then evaluated the damage to each of these tracts in a group of 71 patients with relapse-onset MS, using a pool of advanced MRI techniques: diffusion MRI, magnetization transfer ratio (MTR), and volume quantification. Finally, using principal component analysis and GT, they combined these measures of damage in a single metric for each participant, i.e., the efficiency of the motor network. The authors then showed that this combined metric explained almost 60% of the EDSS variance, substantially outperforming conventional MRI measures of damage such as whole brain T2 lesion load, cervical cord area, or normal-appearing white matter MTR.

While the results of this study need to be replicated in an independent cohort to evaluate the generalizability of this method, the findings presented in the study have some general implications for the development of paraclinical markers of disability in MS.

Current approaches to the evaluation of clinicoradiologic correlations rest on the evaluation of pathology over the whole brain or in single regions of interest (ROIs).[5] These 2 approaches, however, rest on problematic assumptions; namely, that pathology effects on a clinical measure (in this case EDSS) occur irrespective of anatomical localization, or that it is possible to identify the single most important brain region underlying the outcome of interest. It is worth noting that these assumptions are not supported by pathology studies that show distant effects of lesions in functionally connected regions of the brain,[6] by the association between disability and damage in key brain areas,[7] or by the heterogeneity of the results observed in ROI-based studies.[5] The data presented by Pardini et al.,[2] on the other hand, suggest that focusing on brain networks (i.e., a connectivity approach) could allow a useful balance between whole brain and ROI-based approaches, as it enables us to capture pathology in multiple areas relevant for disability without including regions of less relevance.

A second point of interest in this study is represented by its focus on multiple MRI measures. While none of the available MRI techniques is specific for any single facet of MS pathology, none of them is able to capture the whole spectrum of tissue abnormalities observed in this patient population.[5] In line with this, the data presented by Pardini et al.[2] suggest that the combination of different MRI modalities into a single index of pathology substantially improves clinicoradiologic correlations in this patient population. Calls to exploit the power of multimodal data analysis in MS are not new. Still, few investigations and even fewer clinical trials are using one of the many now established analysis techniques. Many readers will find the described methodology challenging. The likelihood is that connectomics and network analysis will become increasingly used in investigations of neurologic diseases. In MS, the promise is that such analyses may help improve the understanding of fatigue, cognitive impairment, and other symptoms not adequately explained by ROI analysis.

The analysis presented is based on structural imaging measures. We know that lesions and the evolution of the disease change how the brain functions. Even in the earliest stages of demyelination, the clinically isolated syndrome, patients have altered resting state networks, possibly due to very early cortical reorganization.[8] If

See page 1115

From the Department of Health Sciences (M.P.S.), University of Genova, Italy; and the Division of Clinical Neurosciences (N.E.), University of Nottingham, UK.

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we can take into account not only the important structural brain nodes but also their function and their reactivity to different stimuli, we should be able to explain more fully the symptoms and disability associated with MS. Functional MRI and magnetoencephalography are likely to play an important role here.

Caution is needed before suggesting the application of this methodology in clinical trials. As the authors acknowledge, more work is needed to verify the robustness of this approach and its applicability to multicenter data. Nevertheless, the approach presented in this study is promising and future studies to validate and expand these results are to be encouraged. In the meantime, it is apparent to us that even busy clinical neurologists need to start learning or continue practicing the language of brain connectivity, which is no longer a language only for psychologists and cognitive neuroscientists.


## STUDY FUNDING

No targeted funding reported.


## DISCLOSURE

M.P. Sormani reports personal fees from Merck Serono, Biogen, Teva, Genzyme, Synthon, Novartis, and Roche outside the submitted work. N. Evangelou reports personal fees from Biogen, Genzyme, and Novartis outside the submitted work. Go to Neurology.org for full disclosures.

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