The challenge of *in vivo* tissue characterization, connectivity and big data

Understanding pathologies and proposing effective treatment strategies can be heavily influenced by the possibility of assessing tissue characteristics *in vivo* with quantitative metrics that are reliable and pathologically meaningful, and can be compared across subjects and between time points. Such metrics can be used to inform hypothesis-driven studies on the functional mechanisms supporting the healthy and diseased brain. They can also be used in selecting patient groups in clinical trials and as *in vivo* biomarkers for monitoring outcomes. Technological advances and powerful computing have contributed to the emergence of the "big data" theory, which allows such metrics to be studied at population level, together with a whole range of other quantitative information from clinical and neuropsychological tests, and fed into algorithms that transform this wealth of information into something personalized and meaningful at single-patient level.

Functional Neurology has decided to dedicate a whole issue of the journal to magnetic resonance imaging (MRI) because of the contribution this technology has made to clinical advances over the past three decades, and in particular to the growing understanding of how the brain works, from its microstructural characteristics to its complex interplay of networks and connections. In fact, the MRI signal can be manipulated to provide information on properties such as neuronal density, which in turn allows the creation of maps that reflect the underlying microstructure. In addition, thanks to the possibility of sensitizing the signal to the diffusion of water in tissue, it has become possible to reconstruct the human connectome and characterize it with global indices that represent its organization and properties at network and whole brain level. Functional MRI contributes to the picture by providing information on synchronous rhythms reflecting functional connectivity or task-induced vascular responses. This functional information can be exploited for network-wise functional connectivity analysis as well as for whole brain connectomics.

Some doubt the ability of MRI to perform detailed as well as precise studies of the human brain *in vivo* because the specificity of MRI "biomarkers" is never absolute. Where there is neuronal loss there is often demyelination, and where there is functional impairment there is often neuronal loss. Therefore, parameters may be affected by several pathological processes, even when reflecting a predominant one. Concerns also arise from the fact that tractography studies reconstructing specific pathways can be affected by a large number of false positives, as has recently been demonstrated. The key message, though, must be that if technical expertise is exploited to address the reproducibility of proposed measures, data are interpreted with caution and consistently with a priori knowledge, and results are reported critically (all principles that were followed in the reconstruction of the cerebello-thalamo-cortical loop in the article by Palesi et al., this issue), then MRI is one of the most powerful methods that we have for accessing the mysteries of the human brain *in vivo*! This is shown by the huge and ever growing impact that MRI is having on patient care, and *Functional Neurology* is keen to contribute to the dissemination of this very important message!

The MRI results of research studies published in this issue will need to be confirmed by future data, and the techniques described will need to undergo further development and validation in several clinical cohorts before they enter clinical practice; but without a pathway-to-impact plan that takes development through pilot studies and research applications, and then verifies the effectiveness of the outcomes, we would not have been able, for example, to develop the methods that now see us relying on MRI for assessing tissue damage related to white matter lesions, vasculature infarcts, tumors and stroke. Although tractography, functional connectivity and microstructure properties are still some way from being used at single patient level, they do not have that far to go either!

This field is moving fast. International consortiums are really pushing for big data generation in order to tackle major clinical needs, such as that of early diagnosis and treatment of dementia. Combining research efforts with practical projects and very specific aims, as proposed by the advanced neuroimaging network of Italy's research hospitals (IRCCS), is the key for fast translation of research tools to the clinic, reflecting the belief that the "whole" is always more powerful than the sum of its parts.

We hope that this issue of *Functional Neurology* will contribute to the evolution and clinical translation of a fascinating research field that has already made a real difference to many, many patients and their families.

Claudia Gandini Wheeler-Kingshott, PhD

Brain MRI 3T Mondino Research Center, C. Mondino National Neurological Institute, Pavia, Italy
NMR Research Unit, Queen Square MS Centre, Department of Neuroinflammation, UCL Institute of Neurology, London, UK
Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy
E-mail: claudia.gandini@unipv.it; c.wheeler-kingshott@ucl.ac.uk

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