In vivo MR imaging of brain networks: illusion or revolution?

Ewald Moser · Jean-Philippe Ranjeva

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Substantial achievements have been made in brain research and the development of non-invasive brain mapping tools such as high-field functional MRI, positron-emission tomography (PET), and the expansion of classical electrophysiological methods like EEG and MEG, as well as the successful combination of such different methods as fMRI & EEG, and MRI & PET. These neuroimaging methods may help to provide a better understanding of the connectivity of large-scale brain networks, opening new insights into how the brain segregates and integrates information. Characterizing basal brain connectivity is a crucial issue, which may lead to a better understanding of brain functioning, and may also allow us to understand, anticipate, and monitor recovery of the clinical consequences of neurological diseases. Nevertheless, we should remind ourselves that we are still looking at the human brain from afar, in the same way an astronaut might view our planet. We observe only the hills or mountain peaks above the clouds (functional connectivity) or major motorways crisscrossing a country (fiber tracking, structural connectivity). Bridging the gap between this coarse global view and local neuronal activity remains challenging.

In this special issue, we have compiled a number of studies, mainly performed in Europe, selected to stimulate efforts in this field. Four reviews and nine research papers are col-

lated, covering various aspects of functional and structural connectivity assessed with MR-based methods.

The first paper is a short historical overview of resting-state fMRI works presented by Mark Lowe, one of the pioneers in the field [1]. After the seminal paper of Bharat Biswal et al. in 1995 [2], the field of so-called ‘resting-state fMRI’ remained controversial until the early 2000’s, when Raichle’s group and others published several influential articles founding the concept of a ‘default mode’ of brain function [3–6]. Other brain networks were also reported, the current total being about 12 [7], a number which seems likely to increase steadily with increasing sensitivity and specificity of the measuring methods. The second paper is a provocative critical review of post-processing methods, which are used to extract relevant (and non-relevant) information from rs-fMRI data [8]. Margulies and colleagues focus on six prominent categories of resting-state data analysis. The coexistence of so many different tools may reflect both limited data quality and a lack of deeper understanding of underlying models of brain function. The main criticism of rs-fMRI is the lack of control of the actual brain status during the so-called ‘resting-state’. One possible solution to overcome this critical problem may rely on the use of simultaneous recordings of brain electrical activity during fMRI. A detailed review of the present applications and perspectives of this method are provided by Rosenkranz and Lemieux [9]. From a methodological point of view, as we are basically looking at ‘brain noise’, increasing the field strength from 1.5 to 3 T and higher, combined with the use of multi-array coils, greatly improves sensitivity. Although this has led to the detection of consistent and reliable brain networks across healthy subjects (e.g. [7, 10]), there are still issues on how to separate physiological noise from relevant information without introducing other artefacts [11, 12]. There is also speculation that physiological fluctuations are a substantial contributor to resting-state

E. Moser (✉)

MR Center of Excellence, Division of MR-Physics,
Center for Medical Physics and Biomedical Engineering,
Medical University of Vienna, 1090 Vienna, Austria
e-mail: ewald.moser@meduniwien.ac.at

J.-P. Ranjeva (✉)

Centre de Résonance Magnétique Biologique et Médicale
UMR CNRS 6612, Université de la Méditerranée,
Faculté de Médecine, 27 Boulevard Jean Moulin,
13385 Marseille cedex 05, France
e-mail: jp.ranjeva@univmed.fr

networks, particularly the default mode network (DMN), as a number of studies have demonstrated overlap between DMN regions and areas of the brain which show BOLD signal variation in response to respiration rate changes and the cardiac cycle (e.g. [11]). Countering these suggestions, Lin et al. have used interleaved perfusion-BOLD and the calibrated fMRI approach to show that the coupling of Cerebral Metabolic Rate of Oxygen and Cerebral Blood Flow is linear in DMN regions—a characteristic of neuronal activation—with a coupling constant that is very close to that in activated regions [13].

In addition to the correlative approaches used in the early studies, exploratory approaches using independent component analysis (ICA) are becoming more frequently employed, allowing non-standard BOLD responses to be pursued more easily. Overlapping brain circuits may also be separated this way, which seems rather important, as the same brain nodes may be active in various circuits. As all these methodological developments are occurring in parallel, it is important for the advancement of the field that numerous groups become involved in this type of research (see e.g. the 2010 scientific program of the annual meetings of ISMRM-ESMRMB in Stockholm, Sweden, and Human Brain Mapping in Barcelona, Spain). This should help to quickly separate useful information from nuisance signal, adding to the scientific rigor and reliability. In the present issue, Schoepf et al. compare the two most commonly used group-ICA toolboxes for analyzing resting-state data [14]. Despite their general usefulness, significant differences are evident and future developments may help to further improve group data analyses (see also [15]). Due to the simplicity of add-on data acquisition for resting-brain studies, quite large data volumes are being collected and the group from Lund presents a method to reduce dimensionality in fMRI time series data via Locally Linear Embedding [16]. The Nottingham group demonstrates the great potential of ultra-high-field fMRI by comparing functional connectivity in the default mode and sensorimotor network at 3 and 7 T [17]. Of course, recent development in high-field MRI enables the reliable mapping of extended functional networks in the human brain and the ability to differentiate between them. When looking closer they are, however, blurred far beyond gray matter boundaries. This may be significantly improved at 7 T [18]. Improved quantitation of functional connectivity increases the reliability of measurements required to compare different populations, and even uses rs-fMRI as a new diagnostic marker of neurological diseases such as Alzheimer's disease [19,20] or epilepsy lateralization [21]. Applications to patient populations to characterize underlying deficits in brain connectivity are also demonstrated in the present issue by Sakoglu et al. in schizophrenia [22]. Furthermore, external modulation of brain connectivity by various levels of sedation, similar to sleep, is demonstrated by Hlinka et al. [23]. They suggest that this

effect may be mediated by increased head motion and, therefore, caution in design, and interpretation of such studies is recommended. Saemann et al. show that functional connectivity may be reduced after partial sleep deprivation with potential consequences in studies and treatment of depression [24].

Looking to other MR methods it is possible, using water diffusion-based signals, to create so-called “fiber tracks”, providing a coarse idea of the direction in which the major structural pathways are organized. In this issue, Mang et al. propose a diffusion simulation-based tracking method using the whole tensor information of a neighborhood of voxels and means to handle problematic tracking situations [25]. Finer traffic routes may also have an important impact on some functional networks. This is the case for the anterior commissure, which constitutes a very important pathway for several functional networks, and one that has been specifically studied by Patel et al. [26].

Finally, another difficulty in rs-fMRI is to be faced by authors in reporting the characteristics of large networks represented by dozens, hundreds, or even thousands of nodes (voxel based approach) connected by thousands of links. Guye et al. review the ways to quantify and unify metrics of network efficiency using graph theory [27]. This approach is also able to merge structural and functional information to globally characterize brain networks using simple metrics for both normal and pathological brains. However, we are still at an early stage in brain network analysis and most of the current techniques do not account for non-linear dynamics of brain functions. It would be highly desirable that the neurosciences should be well advanced when compared to economic research in terms of being able to tell the local and global activity (e.g., gross national product) and the various pathways between them (e.g., traffic routes, money transfer).

As soon as we believe sufficiently reliable data have been acquired [28], we may begin testing and validating brain models. Indeed, structural networks derived from diffusion MRI data are mandatory prior to building computational models that help us to predict neural dynamics at multiple scales [29,30]. It should then become possible to simulate focal lesions and, even more interestingly, their functional consequences on large-scale network efficiency. Simultaneous EEG-fMRI or even sEEG-fMRI may provide crucial information about neurovascular coupling (or decoupling) in more detail, given the high spatial and temporal resolutions available. This should also greatly help with cognitive studies despite the quite challenging experimental setup.

This quest is nevertheless far from being solved, and lots of work, controversial debates, methodological, and theoretical developments as well as progress in computational models merging or using structural information to better track non-linear dynamics of networks are still necessary to provide a clear vision of healthy and pathological brain organization

and function. Mathematics, MR physics, neurosciences, and psychology are currently collaborating to lift several veils and help transform an “illusion” into a revolution in brain network analysis.

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