Longitudinal fMRI studies: Exploring brain plasticity and repair in MS

Christian Enzinger, Daniela Pinter, Maria A Rocca, John De Luca, Jaume Sastre-Garriga, Bertrand Audoin and Massimo Filippi

Abstract: Functional magnetic resonance imaging (fMRI) has greatly advanced our understanding of cerebral functional changes occurring in patients with multiple sclerosis (MS). However, most of our knowledge regarding brain plasticity and repair in MS as evidenced by fMRI has been extrapolated from cross-sectional studies across different phenotypes of the disease. This topical review provides an overview of this research, but also highlights limitations of existing fMRI studies with cross-sectional design. We then review the few existing longitudinal fMRI studies and discuss the feasibility and constraints of serial fMRI in individuals with MS. We further emphasize the potential to track fMRI changes in evolving disease and the insights this may give in terms of mechanisms of adaptation and repair, focusing on serial fMRI to monitor response to disease-modifying therapies or rehabilitation interventions. Finally, we offer recommendations for designing future research studies to overcome previous methodological shortcomings.

Keywords: Multiple sclerosis, fMRI, brain plasticity, brain repair, longitudinal

Date received: 19 September 2015; revised: 25 October 2015; accepted: 4 November 2015

Introduction

Multiple sclerosis (MS) is profoundly heterogeneous regarding its clinical course, neuroradiological appearance, extent and distribution of lesions, and response to therapy. In recent years, considerable progress in cerebral magnetic resonance imaging (MRI) technology has increased our ability to extend assessment of MS-related tissue changes beyond lesions in the white matter (WM), and we can now offer evaluation of the whole brain at a microstructural level. While this was expected to give full insight into the causes of MS patients’ deficits, the current plethora of MRI metrics still provides no complete explanation for the clinical condition at the group level and even less so at an individual level. Functional MRI (fMRI), enabling detection of cerebral functional changes evolving alongside structural changes, has been proposed to partially close this gap.

Since the early, pioneering studies applying fMRI in MS to study functional changes in motor or cognitive domains, technical and analytical possibilities have improved tremendously. fMRI is consequently now established as an important research technique, but our current knowledge on brain plasticity and repair in MS has been mostly extrapolated from cross-sectional fMRI studies in populations with different phenotypes or different levels of disability.

Focusing on the motor system and cognition, this topical review therefore tackles this issue. We first provide an overview of existing cross-sectional and longitudinal fMRI studies in MS, and discuss methodological limitations and challenges. We then highlight the potential to track fMRI changes in evolving disease and the insights this may give in terms of mechanisms of adaptation and repair, specifically addressing the use of serial fMRI to monitor response to disease-modifying therapies or rehabilitation interventions. Finally, we provide recommendations for designing future research studies.

The neurophysiological basis of fMRI

Based on changes in the blood-oxygenation level-dependent (BOLD) signal that are in principle affected by changes in the local balance between neuronal excitation and inhibition, fMRI provides a large-scale (at the millimeter level) average of neural activity. Increased neural activity results in an increased cerebral metabolic

Topical Review

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rate of oxygen and local vasodilation, and thereby increases cerebral blood flow. This in turn reduces the quantity of (paramagnetic) deoxyhemoglobin in the veins, increases local magnetic field homogeneity, and thus enhances the net signal intensity in active (diamagnetic) areas of the brain. With task-related fMRI, within a scan, several periods of active stimulations are contrasted with rest periods, which allow the small signal changes associated with the task under investigation to be captured and statistically modeled. As will be discussed in more detail, studies using this task-associated model have consistently shown abnormal patterns of activation in patients with MS compared to healthy controls, prompting much further work looking to understand what drives the changes seen.10,11

While such studies comparing activation patterns between task performance and rest have been informative, a contrasting approach is to look at fMRI in the absence of a specific task. The increasingly used investigation of resting-state (RS) activity seeks to identify temporally co-varying BOLD signals, which are thought to represent functional connectivity (FC) between different brain regions. As discussed below, this latter approach may circumvent some of the problems related to studies, for example, dependent on motor function in patients with differing levels of motor disability.

Overview of cross-sectional fMRI studies

Studies with fMRI of the cognitive and motor systems have consistently demonstrated abnormalities of brain recruitment in all MS phenotypes, with altered activation of the regions normally devoted to the performance of a given task and/or recruitment of additional areas when compared to healthy subjects. Cross-sectional studies have allowed the characterization of fMRI recruitment in the different stages of the disease, permitting some speculation on the role of functional plasticity in these patients.

It is now established that fMRI abnormalities in MS patients occur relatively early in the disease course, being seen even in patients with clinically isolated syndromes (CISs) and pediatric MS,10 and tending to vary over the course of the disease, not only after an acute relapse but also in clinically stable patients.11,12 The degree of functional brain recruitment above healthy controls is related to the extent and severity of structural central nervous system (CNS) damage in terms of lesions, normal-appearing WM, gray matter, and spinal cord involvement.12 Such correlations suggest that an increased recruitment of “critical” cortical networks might contribute to limiting the functional impact of MS-related damage (i.e. it is a compensatory phenomenon), as cerebral activation changes have also been observed in MS patients without clinically overt deficits.

Rocca et al.’s findings from a cross-sectional study of the motor network in patients with different clinical MS phenotypes support the notion of a “natural history” of brain adaptive mechanisms in MS. This study showed an increased recruitment of those areas “normally” devoted to the performance of a motor task, including the primary sensorimotor cortex and the supplementary motor area, at the beginning of the disease. At a later stage, bilateral activation of these regions was seen, followed by widespread recruitment of additional areas—a pattern seen in healthy individuals only when performing novel or complex tasks. The concept that increasing functional activation for a specific task reflects evolving compensatory mechanisms driven by worsening tissue damage is supported by the observation in pediatric13 and benign14 MS, where a preserved focused and strictly lateralized movement-associated pattern of cortical activations appears to be the rule.

While increased brain activation as a compensatory mechanism may be generally viewed as advantageous, it might not always be beneficial for MS patients and there is also evidence supporting a maladaptive role of functional abnormalities in these patients. Accordingly, in patients with progressive MS,15,16 reduced activation of “classical” regions of the sensorimotor network and an increased recruitment of “high-order” regions (including the superior temporal gyrus bilaterally, the ipsilateral middle frontal gyrus, and the contralateral insula/claustrum) has been found with motor tasks. In cognitively impaired MS patients, a “reallocation” of neuronal resources and inefficiency of neuronal processes have been observed using a working memory rehearsal task (such as increased right prefrontal cortex activation and increased right temporal lobe activation in MS compared to controls, depending on task difficulty).17 Abnormal functional recruitment has also been associated with the presence of fatigue.18

The studies discussed so far have involved comparing activation during a task relative to a control or rest condition. While informative, the assessment and interpretation of fMRI results during active tasks can be difficult when task performance differs across patients. As such, the analysis of RS brain FC is considered a valid alternative to task-active fMRI investigations, particularly in clinically impaired populations. This type of application has shown an increased
RS-FC of the majority of brain networks in CIS patients. In patients with cognitive impairment, reduced RS-FC of frontal lobe regions was related to the severity of cognitive impairment and structural disruption of connecting WM-tracts as assessed by diffusion-tensor MRI tractography. In line with the results from the task-related studies, it remains unclear whether the increased connectivity demonstrated represents a welcome compensatory response or may in itself be maladaptive. In one study by Loitfelder et al., better cognitive performance in MS patients was associated with increased FC among several regions of the attention network, supporting the adaptive role of these modifications. However, findings from other studies seem to contradict the adaptive/compensation hypothesis, showing a correlation between increased RS-FC and worse cognitive performance. Highlighting the complexity of the interpretation of such findings, another investigation focusing on physical disability demonstrated abnormal patterns of intra- and inter-network RS-FC in relapsing-remitting MS (RRMS) patients, which correlated with the extent of T2 lesions and the severity of disability.

The need for fMRI studies with longitudinal design
Despite these achievements, many aspects of brain plasticity still remain to be elucidated. Importantly, the adaptive/maladaptive theory of brain functional reorganization needs to be supported by longitudinal studies, which should ascertain whether functional abnormalities confer a systematic vulnerability to disease progression or, conversely, protect against the onset of clinical deficits. Such longitudinal studies should also try to investigate how fMRI changes are modulated and/or influenced by concomitant or evolving structural MRI damage.

Review of existing longitudinal data
The first longitudinal fMRI study in MS was performed by Reddy et al., who assessed potential functional brain reorganization following an acute MS lesion affecting the corticospinal tract (CST) in a single-case description. They demonstrated dynamic modifications of motor system recruitment, associated with clinical recovery and paralleled by regression of neuronal dysfunction in the CST during 6 months of follow-up. In the same way, Zaaraoui et al. emphasized the existence of long-term (3 years) dynamic processes involving tissue repair and recovery of normal motor functional organization in a patient suffering from an acute large inflammatory-demyelinating lesion affecting the CST. Mezzapesa et al. also evidenced that a favorable outcome in patients suffering from clinical attacks affecting motor function was associated with restoration of normal motor system activation and lateralization.

Dynamic functional reorganization of the motor system in MS may occur even in the absence of significant motor deficits. Pantano et al. investigated the evolution of brain activation generated by a simple motor task in patients after their first clinical attack. They observed increased activation in patients compared to controls at baseline. During follow-up, the activation progressively decreased, but to a lesser extent in patients with worse disease evolution. More recently, the same group demonstrated that a relapse may transiently alter the functional organization of the motor network, independently of the location of the acute lesion.

So far, only a few longitudinal fMRI studies focusing on high-level cognitive systems have been performed in MS. Audoin et al. assessed the evolution of brain activation related to the Paced Auditory Serial Addition Task (PASAT) over a 1-year period in early MS patients. They noted that maintenance of PASAT performance during follow-up was associated with higher activation in the prefrontal cortices. In addition, Loitfelder et al. using a go/no-go paradigm, highlighted that disease progression in RRMS may also be characterized by maladaptive functional reorganization. For an overview of existing longitudinal fMRI studies focusing on motor and cognitive domains in MS, see Table 1.

Tracking fMRI changes in evolving disease—chances and challenges
Disease evolution in MS is associated with progression of WM and gray matter tissue injuries that may induce adaptive and/or maladaptive brain functional reorganization. During the evolution of MS, especially when effective disease-modifying treatment (DMT) or rehabilitation strategies are used, changes in cerebral functional organization may represent a mixture of these processes. Tracking brain functional changes using fMRI may be of value to distinguish between these different processes, although several pitfalls must be overcome before this technique can be applied in clinical trials or even in clinical practice.

The first limitation of task-fMRI relates to the potential confounding effect of task-performance changes on brain activation patterns, that is, in situations when functional impairment itself affects the ability and effort needed to perform a task. This limitation may
### Table 1. Overview of existing longitudinal fMRI studies on motor and cognitive function in MS patients.

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal Year</th>
<th>Patient characteristics</th>
<th>fMRI method</th>
<th>Other MRI metrics</th>
<th>Follow-up period</th>
<th>Intervention</th>
<th>Main finding(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reddy et al.</td>
<td>Neurology 2000</td>
<td>Single patient with RRMS: large lesion of the CST 6 HC</td>
<td>Simple motor task: cued finger-thumb opposition (1.5Hz) versus rest</td>
<td>MRS</td>
<td>6 months, 3 fMRI scans (3, 6, and 24 weeks after relapse)</td>
<td>None</td>
<td>Functional reorganization of the motor system decreased in parallel to the regression of neuronal dysfunction in the CST</td>
</tr>
<tr>
<td>Parry et al.</td>
<td>Brain 2003</td>
<td>8 patients with RRMS and 2 patients with SPMS</td>
<td>Stroop Task</td>
<td>None</td>
<td>24 hours</td>
<td>Administration of a central cholinesterase inhibitor</td>
<td>Study medication reduced the level of brain functional reorganization associated with the Stroop task</td>
</tr>
<tr>
<td>Mainiero et al.</td>
<td>Neurology 2004</td>
<td>12 patients with RRMS</td>
<td>Simple motor task: index-finger to thumb opposition movement</td>
<td>T2-LL, T1-LL</td>
<td>2 scans (receiving 3,4-DAP or placebo) 3 days apart</td>
<td>Administration of 3,4-diaminopyridine versus placebo</td>
<td>A single dose of 3,4-DAP increased recruitment in the ipsilateral sensorimotor cortex and supplementary motor area during a simple motor task in MS patients</td>
</tr>
<tr>
<td>Pantano et al.</td>
<td>Brain 2005</td>
<td>16 patients with RRMS and 2 patients with possible MS 9 HC</td>
<td>Simple motor task: self-paced sequential finger opposition movement</td>
<td>T2-LL, T1-LL</td>
<td>15–26months</td>
<td>None</td>
<td>Age, occurrence of a new relapse, T1-LL at BL and T1-LL changes inversely correlated with changes in reduced motor activation patterns at follow-up</td>
</tr>
<tr>
<td>Audoin et al.</td>
<td>Multiple Sclerosis Journal 2008</td>
<td>13 patients with early RRMS 19 HC</td>
<td>PASAT</td>
<td>T2-LL</td>
<td>12 months</td>
<td>None</td>
<td>Maintenance of PASAT performance was associated with higher activation in prefrontal cortices</td>
</tr>
<tr>
<td>Mezzapesa et al.</td>
<td>Human Brain Mapping 2008</td>
<td>3 patients with RRMS and 3 patients with CIS: pseudo-tumoral lesion of the CST 5 HC</td>
<td>Simple motor task: repetitive flexion-extension of the hand (11Hz)</td>
<td>PD-LL, T2-LL, T1-LL</td>
<td>6 months (monthly examination)</td>
<td>None</td>
<td>Favorable outcome was associated with a restoration of normal activation of the motor system</td>
</tr>
<tr>
<td>Cader et al.</td>
<td>Journal of Psychopharmacology 2009</td>
<td>12 patients with RRMS and 3 patients with SPMS</td>
<td>Stroop task and N-back Task</td>
<td>Lesion volume</td>
<td>2 scans (4 weeks apart)</td>
<td>Administration of rivastigmine and domperidone alone</td>
<td>Rivastigmine enhanced the prefrontal function and altered the FC associated with cognition</td>
</tr>
<tr>
<td>Zaaraoui et al.</td>
<td>Magnetic Resonance Imaging 2010</td>
<td>Single patient with MS: large lesion of the CST</td>
<td>Simple motor task: active motor task, flexion of the hand (11Hz)</td>
<td>MRS, MTR, T2-LL, ADC</td>
<td>3 years (0, 3, 11, 29, 59, and 169 weeks)</td>
<td>None</td>
<td>Long-term functional, structural and metabolic changes were present in the motor system following a relapse</td>
</tr>
<tr>
<td>Pantano et al.</td>
<td>Multiple Sclerosis Journal 2011</td>
<td>32 patients with RRMS including 19 patients within 48 hours of relapse onset: sensory motor (6), cerebellar (5), multifocal (8)</td>
<td>Simple motor task</td>
<td>None</td>
<td>30–50 days</td>
<td>None</td>
<td>Relapse transiently altered functional motor network organization, independently of location of the acute lesion</td>
</tr>
<tr>
<td>Sastre-Garriga et al.</td>
<td>Multiple Sclerosis Journal 2011</td>
<td>3 patients with RRMS: 2 patients with PPMS and 10 patients with SPMS</td>
<td>PASAT</td>
<td>None</td>
<td>5 weeks</td>
<td>Cognitive rehabilitation (computer and non-computer aided)</td>
<td>Rehabilitation was associated with an alteration of the activation pattern related to the PASAT, characterized by higher activation of the cerebellum</td>
</tr>
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<tr>
<th>Author</th>
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<tr>
<td>Chiaravalloti et al.</td>
<td>Journal of Neurology 2012 and Leavitt et al. Brain Imaging and Behavior 2014</td>
<td>11 patients with RRMS and 5 patients with SPMS Word learning task, word recognition task, and resting-state fMRI</td>
<td>None</td>
<td>5 weeks</td>
<td>Memory rehabilitation</td>
<td>Memory rehabilitation induced activation changes mainly in frontal and temporal regions and increased FC in the hippocampal memory network and the default network</td>
<td></td>
</tr>
<tr>
<td>Filippi et al.</td>
<td>Radiology 2012</td>
<td>20 patients with RRMS Stroop task and resting-state fMRI</td>
<td>GM volumes and WM architecture</td>
<td>12 weeks</td>
<td>Computer assisted cognitive rehabilitation of attention, information processing and executive functions</td>
<td>Rehabilitation was associated with significant functional reorganization in brain regions involved in executive control but not with brain structural changes</td>
<td></td>
</tr>
<tr>
<td>Cerasa et al.</td>
<td>Neurorehabilitation &amp; Neural Repair 2013</td>
<td>23 patients with MS PASAT</td>
<td>T2-LL</td>
<td>6 weeks</td>
<td>Computer-based attention training</td>
<td>Rehabilitation was associated with an alteration of the activation pattern related to the PASAT, characterized by higher activation of the cerebellum and parietal cortex</td>
<td></td>
</tr>
<tr>
<td>Parisi et al.</td>
<td>Multiple Sclerosis Journal 2014</td>
<td>18 patients with RRMS Resting-state fMRI</td>
<td>None</td>
<td>12 weeks</td>
<td>Computer assisted cognitive rehabilitation of attention, information processing and executive functions</td>
<td>Changes in resting-state FC of cognitive-related networks helped to explain the persistence of the effects of cognitive rehabilitation after six months in patients with RRMS</td>
<td></td>
</tr>
<tr>
<td>Lotfielder et al.</td>
<td>PLoS ONE 2014</td>
<td>13 patients with RRMS 15 HC Go/no-go task response discrimination task</td>
<td>NBV Subcortical GMV Cortical thickness T2-LL Annualized BVC</td>
<td>12–20 months</td>
<td>None</td>
<td>Maladaptive functional reorganization occurred during disease progression, indicated by increasing parietal activation that correlated negatively with processing speed</td>
<td></td>
</tr>
<tr>
<td>Hubacher et al.</td>
<td>Restorative Neurology and Neuroscience 2015</td>
<td>5 patients with juvenile MS N-back task</td>
<td>None</td>
<td>4 weeks</td>
<td>Computerized working memory training</td>
<td>Beneficial effect of working memory training was associated with significant reorganization in the working memory network and with an enhancement of inter-networks connectivity</td>
<td></td>
</tr>
<tr>
<td>Bonavita et al.</td>
<td>Journal of Neurology 2015</td>
<td>18 cognitively impaired patients with RRMS Control group: 14 cognitively impaired patients with MS</td>
<td>Resting-state fMRI NBV T2-LL</td>
<td>8 weeks</td>
<td>Computer-based cognitive rehabilitation (intervention group) or unspecified cognitive training (control group)</td>
<td>In cognitively impaired RRMS patients, computer-based cognitive rehabilitation improved cognitive performances, and increased FC in the PCC and inferior parietal cortex of the DMN</td>
<td></td>
</tr>
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</table>

MS: multiple sclerosis; fMRI: functional magnetic resonance imaging; 3,4-DAP: 3,4-diaminopyridine; ADC: apparent diffusion coefficient; BL: Baseline; BVC: brain volume change; CST: corticospinal tract; DMN: default mode network; FC: functional connectivity; GM: gray matter; GMV: gray matter volume; HC: healthy controls; LGN: lateral geniculate nucleus; LL: lesion load; LPFC: lateral prefrontal cortex; MRS: MR spectroscopy; MTR: magnetization transfer ratio; NAA: N-acetylaspartate (a marker of neuronal integrity); NBV: normalized brain volume; ON: optic neuritis; PASAT: Paced Auditory Serial Addition Task; PCC: posterior cingulate gyrus; PD: proton density; RRMS: relapsing-remitting MS; SPMS: secondary progressive MS; WM: white matter; CIS: clinically isolated syndrome.
be overcome using a very simple fMRI task that can be performed normally by patients irrespective of their disability level. However, this approach prevents the assessment of potential reorganization occurring in neuronal networks involved in more complex cognitive systems which, in turn, appears of particular interest in MS where deficiencies in high-order information processing frequently occur.

In this context, RS-fMRI methods may prove valuable. Nevertheless, while the ability to depict subtle functional changes using the RS-approach has been demonstrated in cross-sectional studies, the interpretation of such findings remains speculative, particularly concerning the distinction between adaptive and maladaptive processes. Indeed, while this distinction is now rather well characterized for the motor system based on numerous task-related fMRI studies in MS and other neurological diseases like stroke, this holds less true for higher level cognitive systems. As a matter of fact, a refined understanding of functional reorganization in higher level cognitive systems requires longitudinal fMRI studies in large patient samples with homogeneous clinical phenotypes and accurate tissue injury characterization. Finally, it is critical to obtain normative data regarding the natural evolution of functional brain organization across the normal lifetime, in order to confidently apply such approaches to patient groups or even individual patients.

**Serial fMRI to monitor response to medical treatment or rehabilitation intervention**

The potential influence of drug administration or rehabilitation interventions on functional brain reorganization has been examined in several studies. Two studies from a UK group demonstrated that acute and chronic administration of a central cholinesterase inhibitor led to modifications of the patterns of activations and FC of cognitive networks in patients with MS. In a separate study, Mainero et al. observed that a single dose of 3,4-diaminopyridine resulted in increased recruitment in the ipsilateral sensorimotor cortex and supplementary motor area during a simple motor task in MS patients. Regarding the impact of cognitive rehabilitation on brain function in MS, Sastre-Garriga et al. demonstrated altered activation patterns related to the PASAT task, characterized by increased cerebellar activation, and Cerasa et al. reported similar findings. Chiaravalloti et al. showed that memory rehabilitation in MS patients induced activation changes mainly in frontal and temporal regions and increased RS-FC in the hippocampal memory network and default mode network. In pediatric MS, Hubacher et al. demonstrated beneficial effects of working memory training, including significant reorganization in the working memory network and enhancement of inter-network connectivity. Filippi et al. used task-related and RS-fMRI to study functional brain changes after computer-assisted cognitive...
rehabilitation of attention and executive functions. Both approaches identified significant functional reorganization in brain regions implicated in executive control, which were associated with improvements in neuropsychological tests.

Despite increasing research efforts on objective, longitudinal assessment of the impact of motor and cognitive rehabilitation approaches in MS using fMRI, several issues remain unsolved. Among these, the confounding effect of different task performance across individuals is particularly relevant, since fMRI activity alterations may be due to performance changes related to disease progression and not the intervention itself. Moreover, improved designs should include patients with, at least, moderate impairment to perform such tasks. This poses challenges especially for task-related fMRI, for example, considering that performing a PASAT-fMRI task might be relatively easy for patients with CIS, yet demanding for patients with moderate to severe cognitive impairment. With its own limitations, as mentioned earlier, RS-fMRI is one approach to overcome disease progression–related changes in task performance over time and has thus been increasingly used recently.

While rehabilitation-induced changes in RS-FC have predicted a positive clinical evolution over time, the long-term persistence or behavioral effects of such alterations are still unknown. However, this would help disentangle the adaptive versus maladaptive conundrum. Finally, until the relationship between functional changes and tissue injury is better understood and described, interventional studies should be short (e.g. a few weeks to months) to avoid the (still difficult to adjust for) differential accumulation of structural damage across patients. This limitation severely hampers the use of fMRI in longer rehabilitation therapy programs and, obviously, in studies aiming to assess the effect of disease-modifying therapies.

The feasibility and constraints of serial fMRI within individuals with MS

High reproducibility of fMRI data is crucial for its application in clinical studies. Recent studies have confirmed that in healthy subjects, serial (motor and cognitive function) task-related and RS-fMRI are highly reliable, even across different sites. Although reproducibility in MS patients is lower compared to controls, fMRI data have been shown to be sufficiently reproducible to detect changes with only modest effect in patient samples. Furthermore, reproducibility can be optimized by specifications concerning the study protocol and analytical approach (e.g. use of short MRI protocols to avoid fatigue, exploring more sophisticated measures of brain response to maximize intra-individual reproducibility, and including additional parameters to optimize reproducibility). Together, these findings are encouraging regarding the prospect of using fMRI in the longitudinal assessment of large multisite cohorts of early MS patients, even if followed for many years.

A major challenge of serial fMRI remains the exploration of the complex relationships between motor and/or cognitive function and functional brain changes, as various possible and mutually interacting determinants need to be considered in patients with MS (Figure 1). With all these considerations, the array and extent of examinations (e.g. MRI protocol, assessments, questionnaires, etc.) still have to provide a tradeoff between feasibility in the clinical setting and scientific endeavor, as this is crucial to ensure compliance and avoid drop-out.

Another critical issue for longitudinal studies in MS is how to handle data of patients with relapse or subclinical disease activity or with changes in medication. Also, bias of sample selection needs to be considered, as severely impaired patients will most likely discontinue participation in scientific studies or may not be recruited in the first place. Notwithstanding these limitations and others that cannot be addressed in this review, serial fMRI in patients with MS now has become feasible and appears a promising method to assess functional reorganization related to disease progression and/or treatment.

Conclusion

In this topical review, we argue for the need of longitudinal studies including structural and functional MRI in large cohorts of early MS patients followed for many years to increase our understanding of the mechanisms of functional (mal)adaptation in MS. We also offer suggestions for the design of such studies (Box 1). Whether this will finally permit an evaluation of the capacity for adaptation at the individual level remains unclear. However, such an endeavor appears worthwhile, given the potential of serial fMRI to decipher at least part of the considerable clinical heterogeneity of this challenging disease and, moreover, to monitor the brain’s response to disease-modifying therapies or rehabilitation interventions.
Box 1. Suggestions for designing future longitudinal fMRI studies in MS.

- Study large cohorts of early MS followed for many years (preferably in multi-center settings)
- Investigate how fMRI changes are modulated and/or influenced by concomitant or evolving structural brain damage assessed both by conventional and non-conventional MRI
- Strive for inclusion of clinically homogeneous disease phenotypes
- Comprehensively assess demographic, clinical, motor and neuropsychological parameters to allow interpretation of the clinical significance of MRI changes
- Assess and analyze task-related and RS-fMRI in parallel to help disentangle the “adaptive versus maladaptive conundrum”
- Use simple fMRI tasks that can be performed normally by patients irrespective their level of disability to avoid confounding effects of task performance or include task performance as covariate in fMRI analyses
- Include comprehensive structural and functional imaging in interventional studies to control for accumulation of structural damage possibly influencing treatment outcome
- Obtain data on the reproducibility and repeatability of the MRI parameters over time in healthy controls
- Obtain normative data regarding the natural evolution of functional brain organization across normal lifetime

MS: multiple sclerosis; RS-fMRI: resting-state functional magnetic resonance imaging.

Acknowledgements
The initial conception of this topical review was done by C.E. and critically revised by all authors. The Abstract, Introduction, and Conclusion were written by C.E. The sections “Overview of cross-sectional fMRI studies” and “The need for fMRI studies with longitudinal design” were written by M.A.R., M.F., and C.E. The sections “Review of existing longitudinal data” and “Tracking fMRI changes in evolving disease-chances and challenges” were written by B.A. and C.E. The section “Serial fMRI to monitor response to medical treatment or rehabilitation intervention” was written by J.S.-G., B.A., and J.D.L. The section “The feasibility and constraints of serial fMRI within individuals with MS” and the figures were generated by D.P. and C.E. The table was generated by D.P. and B.A. The box “Suggestions for designing future longitudinal fMRI studies in MS” was done by all authors. All authors revised the manuscript for important intellectual content and approved the final version of this paper.

Conflict of interest
C.E. has received funding for travel and speaker honoraria from Biogen, Bayer Schering Pharma, Merck Serono, Novartis, Genzyme, and Teva Pharmaceutical Industries Ltd./sanofi-aventis; research support from Merck Serono, Biogen, and Teva Pharmaceutical Industries Ltd./sanofi-aventis; and is serving on scientific advisory boards for Bayer Schering Pharma, Biogen, Genzyme, Merck Serono, Novartis, and Teva Pharmaceutical Industries Ltd./Sanofi-Aventis. D.P. has nothing to disclose in relation with this article. M.A.R. received speaker honoraria from Biogen Idec, Novartis, Genzyme, and ExCemed; and receives research support from the Italian Ministry of Health and Fondazione Italiana Sclerosi Multipla. J.D.L. serves on an advisory board to Biogen Idec, has received research funding from Biogen Idec, and serves as a speaker for EMD Serono. J.S.-G. has received compensation for serving on scientific advisory boards or in speaker’s bureaus from Biogen, Merck Serono, Novartis, Teva, Almirall, and Sanofi-Aventis. He serves in the editorial board of Multiple Sclerosis Journal. B.A. has nothing to disclose in relation with this article. M.F. serves on scientific advisory boards for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Bayer Schering Pharma, Biogen Idec, Merck Serono, and Teva Pharmaceutical Industries; and receives research support from Bayer Schering Pharma, Biogen Idec, Merck Serono, Teva Pharmaceutical Industries, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer’s Drug Discovery Foundation (ADDF), and the Jacques and Gloria Gossweiler Foundation (Switzerland).

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

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