Functional plasticity in MS

Friend or foe?

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MRI is an irreplaceable tool for diagnosing and monitoring multiple sclerosis (MS). Indeed, conventional MRI is very sensitive in detecting focal, macroscopic white matter lesions of the CNS. This has led to the formulation of diagnostic criteria, which rely not only on the neurologic assessment, but also on MRI markers. Similarly, conventional MRI is also used worldwide to monitor natural MS evolution, or to monitor specific treatment strategies. Recently, research has tried to broaden the horizon of MRI applications in MS beyond lesion detection.[1] In this context, diffusion tensor imaging studies have shown that patients with MS experience microstructural tissue abnormalities that extend well beyond focal lesions.[2] However, the relationship between structural damage to distributed hardwired brain networks and functional changes that are also known to occur in patients with MS is still unclear. In agreement with the fact that the human brain can undergo plastic changes, several studies have shown that patients with MS experience a modulation of their activation patterns following structural tissue damage.[3–6] Such a functional reorganization mainly consists of increased activation of regions that are devoted to a given task and recruitment of additional areas that may or may not be part of the same network. These functional changes are thought to have a compensatory role, thus possibly explaining the weak relationship between MRI-detected tissue damage and patient clinical manifestations.

fMRI offers a unique opportunity to investigate the brain's response to structural damage, either using specific task paradigms or at rest. The majority of fMRI studies in MS have been based on the performance of motor tasks.[3] These have shown an increased recruitment of the motor cortex and an additional recruitment of supplementary or "high-order" motor areas. Cognitive tasks have also been used to assess functional reorganization in MS. For example, during a declarative memory task, hyperactivation of parahippocampal areas has been detected in cognitively normal patients, whereas hypoactivation occurs in patients with cognitive impairment.[4] Interestingly, studies in cognitive rehabilitation in MS are increasing and have shown functional changes of "critical" brain networks following rehabilitative intervention.[5,6]

Resting-state fMRI may also be used to study MS and other neurologic conditions. At rest, specific neural networks are active, such as the so-called default mode and visual processing networks.[7] Since no task paradigm is used, resting-state fMRI studies typically measure the amount of coherent (i.e., synchronous) activity that occurs between different brain areas, also known as functional connectivity. In relapsing MS, some brain areas tend to communicate more synchronously with each other than in healthy controls. Typically, this is not always associated with an increased activity of these areas. In other words, this resembles a situation in which 2 individuals deliver similar sentences without increasing the volume of their voices. This is the fundamental difference between task-based and resting-state fMRI studies. Interestingly, increases of functional connectivity that have been found in MS are related to a poor cognitive performance.[8,9]

In this issue of *Neurology*®, Gallo et al.[10] present the results of a resting-state fMRI study that focused on the visual processing network in MS. The study investigates whether functional reorganization takes place in this network in response to structural damage. They enrolled 2 groups of patients with MS: one with a history of optic neuritis, one of the most common manifestations of MS, and another without. While both groups showed overall reduced correlation strengths within the visual network, patients with a history of optic neuritis experienced an increased functional connectivity compared to those without. The number of optic neuritis episodes was related to the level of increased functional connectivity within extrastriate visual areas. As is the case for any cross-sectional imaging study, however, deter-

mining causality of the reported abnormalities is impossible. Although it is plausible that structural damage to the optic nerves could be the *primum movens* of the observed functional changes of the visual network, longitudinal studies from the earliest disease phase onward are now warranted to elucidate whether such changes have a compensatory role.

The study by Gallo et al.[10] is an important step forward in the field, since it suggests that structural damage to specific brain structures is likely to alter functional connectivity patterns of the corresponding networks at rest. The meaning of these functional changes, however, remains unclear since it can be interpreted in 2 opposite ways. On the one hand, it may reflect the occurrence of adaptive mechanisms with the potential to return the network to "normal" function, which in turn might limit the clinical consequences of tissue damage. Conversely, it may also just be a mere "side effect" of a reduced structural connectivity. In this case, functional reorganization can be viewed as a result of network dysfunction, caused, for example, by an injury to inhibitory interneurons. In this latter case, the resulting hyperactivation or hypersynchronization of structures could be without any positive clinical effect, or could even be associated with the development of additional symptoms and signs.

There are key unanswered questions remaining: Does functional reorganization improve patient functioning and should it therefore be promoted? Or, alternatively, is functional reorganization a negative "side effect" of tissue damage and, thus, should it be avoided? Clearly, a definitive answer to these questions would dramatically improve our understanding of MS pathophysiology and would inform better treatment strategies for these patients. This fascinating field of research will benefit from improvements of MRI methodology and future longitudinal studies. The available fMRI data in MS, including those presented in this issue of *Neurology*, have the unquestionable merit of bringing functional reorganization to the attention of the MS community.

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