Functional magnetic resonance imaging in the study of multiple sclerosis

Tomás Labbé, Ethel Ciampi, Juan P. Cruz, Mariana Zurita, Sergio Uribe, Claudia Cárcamo

Introduction. Multiple sclerosis (MS), a neuroinflammatory and demyelinating disease, modifies the normal connectivity among different brain regions involved in specific functions. Functional magnetic resonance imaging (fMRI), based on local changes in oxygen level as a response to the increase in neural activity, provides an approach to neural connectivity and brain dynamics which give us an overview on visual, motor and cognitive dysfunction and their mechanisms.

Development. An advanced search was performed using PubMed. Terms 'fMRI', 'visual', 'motor', 'cognitive' and 'multiple sclerosis' included in title and abstract were considered. We focus on original articles available in English. Articles were included based on their abstracts, looking for those potentially useful for understanding functional changes in MS. An important amount of studies have used fMRI as a complementary tool in the study of MS and clinically relevant alterations compromising visual, motor and cognitive domains. Since the earliest stages of the disease, local activity, and global neural dynamics appear to be compromised. Even when functional performance is still preserved, a different recruitment of neural resources arises as a compensatory response to disconnection observed in the disease.

Conclusions. The main findings of fMRI applied to MS are strongly related to the demyelinating nature of the disease and provide an adequate insight into the mechanisms that underlie functional alterations reported in this disease. fMRI also appears to be useful for studying disease evolution and response to treatment in MS and other disorders.

Key words. fMRI. Functional neuroimaging. Multiple sclerosis. Nervous system disease. Neurodegenerative diseases. Neuroimaging.

Interdisciplinary Center of Neurosciences (T. Labbé, C. Cárcamo); Neurology Department, Faculty of Medicine (E. Ciampi); Radiology Department, Faculty of Medicine (J.P. Cruz, S. Uribe); Biomedical Imaging Center (M. Zurita, S. Uribe); Pontifical Catholic University of Chile. Faculty of Medicine; Universidad San Sebastian (T. Labbé). Santiago, Chile.

Corresponding author:
Dra. Claudia Cárcamo Rodríguez. Neurology Department. School of Medicine. Pontifical Catholic University of Chile. Marcoleta, 350, 2.º. Santiago, Chile.

E-mail:
esclerosismultipleuc@gmail.com

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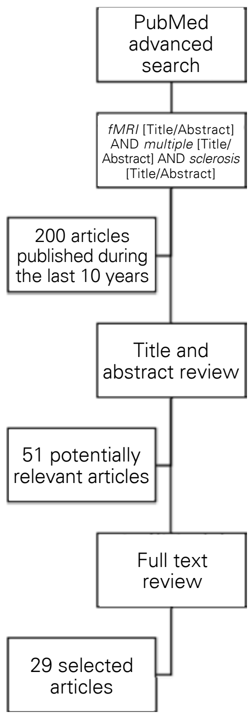
Introduction

When a brain region is involved in the performance of a specific task, its neuronal activity generates changes in the blood oxygen level dependent (BOLD) signal. These changes are measurable under specific sequences of magnetic resonance imaging [1,2].This kind of acquisitions are known as functional magnetic resonance imaging (fMRI) and the variations in the intensity of their signal are due to the changes in the relation between oxygenated and deoxygenated hemoglobin in the brain blood vessels as a consequence of the increase in oxygen income triggered by different metabolic mechanisms both of neuronal and astrocytic origin [3,4]. Neural activity can be studied both in resting state and during motor or cognitive tasks. Despite the existence of certain agreement regarding the BOLD signal basis, there rare different approaches to the analysis of the fMRI data. In these approaches, the concepts of functional and effective connectivity are frequently applied. The first is related to the correlation measures between the variations in BOLD signal taken from different brain regions and the second one is related to the causal effect of a cortical region over another [5,6]. In the same line, the brain activity can be decomposed into a series of independent components determined by activity changes in a coordinated shape across the time [7-9] or as a sum of nodes interconnected by axis [5]. Some of them are so highly connected and influential over the brain dynamic that has been called as 'rich club' organization [10,11].

Under the theoretical construct previously shown, fMRI has provided abundant evidence regarding the underlying mechanisms of neurologic and neuropsychiatric diseases as depression [12] or schizophrenia [13], and the neural mechanisms related to their response to treatment [14].

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease characterized by the loss of myelin in the white matter and eventually axonal loss [15,16]. So, many of its manifestations have been attributed to the development of a disconnection syndrome. Indeed, from the neuroimaging perspective, both structural –diffusion tensor imaging (DTI)– and functional connectivity approaches have shown to coexist and give a report of dis-

Figure 1. Flowchart of the search strategy.



connection underlying disability and cognitive changes [17]. Beyond its potential to generate disability in young people, one of the most interesting issues in MS is that 40-70% of patients develop some level of cognitive impairment [18] despite de wide variability in lesion load and brain atrophy.

The main objective of this article is to provide an insight on how fMRI has contributed to the understanding of the impact of MS in different functional systems and how it could be useful for being applied to the study of other diseases.

Development

An advanced search was performed using PubMed web platform. The terms 'fMRI', 'multiple' and 'sclerosis' as included in title and abstract were considered to perform the search. Only articles published during the last ten years were considered. Nevertheless, some older articles regarding MS or fMRI technique are mentioned in order to provide conceptual context. A list of 200 articles was initially obtained. All of them were classified as potentially relevant or irrelevant for this systematic review based on its title and abstract. 71 potentially relevant articles were analyzed (considering full text) and finally 51 articles were included. After full text analysis, we included 29 articles evaluating clinically relevant functions (as visual, motor and cognitive abilities) through an experimental design based on fMRI acquisitions. We also included resting state studies in MS patients. Articles not including fMRI, or those developed in other clinical populations were excluded. Figure 1 shows the flowchart of the strategy for search and include articles. A considerable amount of additional articles are cited in the text with explanatory purposes, most frequently in the introductory paragraphs and in the contextualization of resting state fMRI.

Task-related fMRI

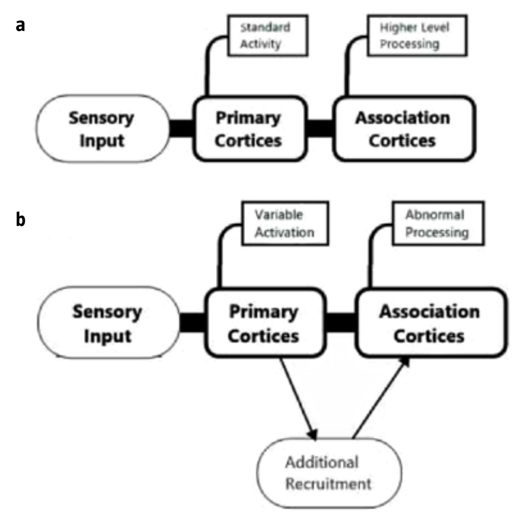
Probably, the most solid conclusion derived from fMRI studies in MS is related to the existence of cortical reorganization occurring in patients [19]. Nevertheless, as clinical and structural findings differ among MS subtypes, the related fMRI findings must vary between relapsing remitting (RR) and progressive forms of the disease. Even if counterintuitive, cortical plasticity is not always related to good news. In the following paragraphs, we discuss evidence regarding neural plasticity responses in neural systems commonly affected in MS patients.

Visual system

One of the first protocols investigating changes in the visual system in MS using fMRI applied a monocular photic stimulation to seven patients who had recovered from a unique episode of unilateral optic neuritis. They showed higher activation of the visual network including claustrum, posterior and lateral parietal cortex and thalamus besides the activation of primary visual cortex when stimulating the affected eye. Interestingly, when stimulating the unaffected eye, only insula, claustrum and primary visual cortex were activated. These findings were strongly related to the latency of visually evoked potentials, suggesting cortical reorganization may represent an adaptation to permanently abnormal input [20]. Additional research has supported this idea [21] and supplemented the whole picture by reporting a decrease in the activation of the primary visual cortex [22]. Taken together, this evidence establishes a general mechanism by which brains react to a demyelinating lesion to compensate functional alterations: a decrease in the participation of primarily involved brain areas and a compensatory increase in the recruitment of non-related regions.

The dynamic functional recovery after an episode of optic neuritis has been also studied. Korsholm et al followed 19 patients during six months after the first clinical episode of MS, and reported significantly lower activation of the lateral cingulate nucleus in the acute phase when visual stimulation was applied. Furthermore, this difference between eyes decreased during recovery and finally disappeared during the follow-up [23]. This has been interpreted as early plasticity phenomena. Even if a dynamic behavior of neural plasticity event has been established, its temporal profile during the disease evolution and its contribution to preservation or impairment in different functions still remain undefined. Figure 2 shows a schematic representation of both normal and abnormal processing of visual input in MS.

Figure 2. Schematic comparison of input processing. a) Normal sensory input processing involving primary and association cortices in a well limited way; b) In an injured brain as in multiple sclerosis, a sensory input generates variable activation of primary cortices and then abnormal recruitment of association cortices leading to abnormal perception or interpretation of input.



Motor system

When considering the motor system, the notion of adaptive or maladaptive plasticity arises again. When comparing motor-impaired MS patients with those motor-preserved groups, both considering RR and progressive patients, fMRI has allowed establishing differences from the perspective of neural networks. Those patients with preservation of motor skills have shown higher functional connectivity in visual processing areas and patients with motor impairment show lower levels of functional connectivity in somatosensory association cortices, even in the absence of significant differences in lesion load [24].

On the other hand, the study of motor functions during fMRI recordings has provided evidence of disorganization in brain cortex since the earliest stages of the disease. A group of patients with clinically isolated syndrome was followed during a year in order to compare cortical activity patterns in those who remain under the diagnosis of clinically isolated syndrome and those who progress to MS. Non progressive subjects showed higher activation of areas integrating motor network while the progressive group showed higher activity in several frontal, parietal, temporal and occipital areas [25]. Even if a higher recruitment of cortical surface can contribute to limit the impact of structural damage during the MS natural history, the early activation of those mechanisms could produce an early consumption of the brain's adaptive properties [19], commonly observed in patients with a more progressive phenotype.

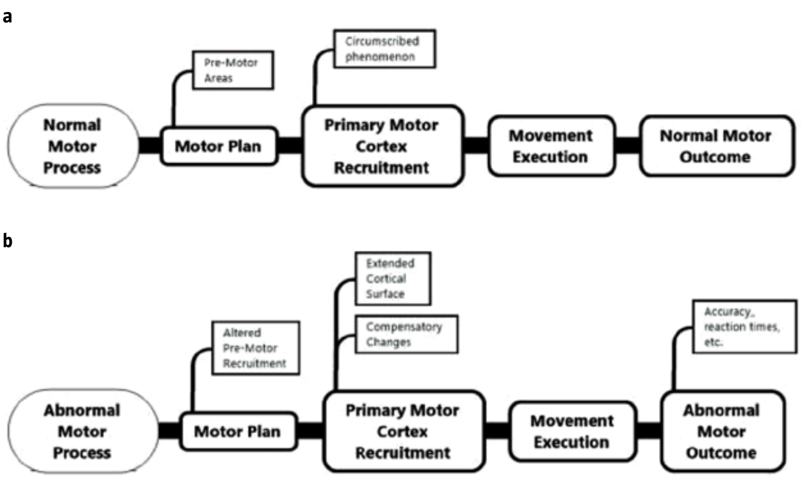
The fatigue, a major clinical event in MS [26], has been also evaluated under fMRI paradigms. The subjective levels of fatigue have been related to changes in the cortical activity of certain areas as caudate, putamen, pallidum, thalamus and amygdala during demanding motor tasks and in relation with rest periods in RR with minimal levels of disability as measured by the Expanded Disability Status Scale [27]. In the same line, it has been demonstrated that in fatigued patients, executive and motor areas exhibit abnormal activation during motor tasks requiring prolonged effort [28]. These findings suggest that alterations in the activity of motor and non-motor areas are related with the appearance of fatigue as an important symptom of MS, identifying it as a complex phenomenon with a basis in the neural dynamics.

Figure 3 shows a schematization of normal and abnormal motor process since planning to execution.

Cognitive functions

In the current management of the disease, cognitive dysfunction represents a big therapeutic challenge, especially considering that in early stages of the disease, more than 50% of patients will exhibit some significant cognitive dysfunction [29-31]. As in other neurodegenerative diseases, the pattern of cognitive decrease in MS is relatively well known and affects specifically working memory, processing speed

Figure 3. Schematic comparison of normal and abnormal motor processes. a) In a healthy brain, after a specific motor planning, a circumscribed participation of motor cortices leads to an accurate motor performance; b) In a brain with altered networks all steps, since planning to execution of movement can lead to an abnormal motor outcome.



[32], verbal fluency and executive functions [33]. The compromise of these functions directly affects daily living skills [34] and social functioning [35].

Considering this profile, studies using fMRI and Paced Auditory Serial Addition Test working memory test in early stages of the disease have shown that a preserved performance in the task is related to a higher activation of frontopolar, prefrontal and cerebellar cortices [36] and Brodmann areas 44 and 45 [37]. This provides evidence about how, even in cognitively preserved subjects, changes in neural resources involved in specific functions can be found [38], both by the higher recruitment of non-related areas, as supplementary motor cortex during working memory tasks [39] or by changes in activity properties of regions highly related to cognitive functions, as centrality measures of default-mode network (DMN) regions [40]. In the same line, since early stages of the disease alterations in how brain answer to an increase in cognitive demands has been demonstrated [41,42]. It adds complexity to the cognitive study of those patients because some alterations may remain at a subclinical level depending on cognitive demands of the environment.

Additionally, the impact of cognitive rehabilitation on the functioning of neural networks has also been studied using fMRI. Subjects included in this kind of management have reported improvement in processing speed performance and higher activation of prefrontal and temporoparietal regions [43], providing an objective neurodynamic basis to evaluate the response to this or another kind of treatments.

Social cognition domain has recently become a focus of interest for MS teams and fMRI has been a useful tool in this area. When face expressions recognition tasks have been applied, differences in cortical recruitment have been found among disease phenotypes [44].

Resting-state fMRI in MS

The study of the BOLD signal in absence of cognitive or motor tasks has allowed obtaining a view of the intrinsic functional architecture of human brain. Interestingly, some studies in free task conditions have reported that spontaneous neural activity does exist in a group of cortical and subcortical regions in different locations but functionally related, including visual, motor and cognitive control areas [45,46]. If we pay attention to this last group, using posterior cingulate cortex as a region of interest, there are regions in which resting state signal is positively correlated, as medial prefrontal cortex, and negatively correlated as intraparietal sulcus, frontal orbital fields and medial temporal regions [47]. Thus, the brain is intrinsically organized into networks operating even in absence of an overt cognitive or motor behavior.

Some of the most commonly considered resting state networks both in the study of healthy and disease populations would be: auditory and language processing, visual processing, executive functioning, sensorimotor network, attentional network, default mode network, right frontoparietal network, and left frontoparietal network [48-55]. Figure 4 shows examples of resting state networks on healthy subjects.

Despite the big amount of information derived from fMRI acquisitions, the accuracy of its interpretations depends on an adequate data processing and analysis. Two of the most frequent approaches to the study of brain connectivity beyond the local changes in BOLD signal are independent component analysis (ICA) and graph theory. In the first case, ICA decomposes the brain dynamics into spatial maps of regions with correlated changes in neural activity during the time [7]. In the other hand, graph theory evaluates the influence of brain regions over other areas or over the entire brain and describe each region of interest –or nodes– using terms as the degree of a node, clustering, modular organization and global efficiency to characterize the influence of each node on close and distant regions [5].

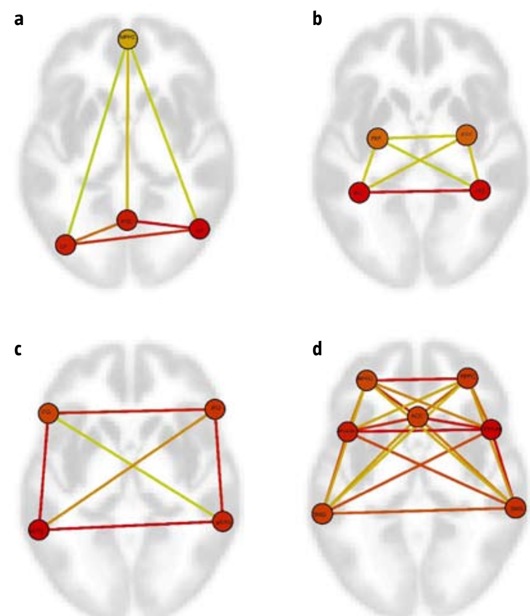
In the specific case of MS, resting state fMRI (rs-fMRI) has provided a higher degree characterization of correlation between structural disconnection, as measured by DTI and functional changes [17]. Also, it has contributed to understanding the network reorganization following the initial appearance of an acute lesion [56]. When considering temporal evolution of functional connectivity compensations, a global pattern has been established. An initial enhancement of brain connectivity decreases during the disease course and this decrease is related to disability progression [57]. Also, some specific functional connectivity patterns, as those alterations in anterior cingulate cortex, often characterize clinically isolated syndrome patients who progress to RR MS [58]. As a view to the different stages of the illness, 14 patients with clinically isolated syndrome, 31 patients with RR MS and 41 healthy controls were studied. Clinically isolated syndrome patients showed increased synchronization in six of the eight identified resting state networks, including the DMN and sensorimotor network, compared to controls or RR MS patients. When the disease progresses, no significant resting state synchronization differences were found between patients and controls, suggesting that this specific cortical reorganization of resting state networks is an early and finite phenomenon in MS [59].

Even if the previously described study reported that resting state networks changes were limited to the clinically isolated syndrome stage, in a different experimental design including 13 patients with RR MS patients and 14 matched healthy controls, ICA provided eight consistent neuronal networks involved in motor, sensory and cognitive processes and for seven resting state networks, the global level of connectivity was significantly increased in patients compared with controls. Interestingly, no significant decrease in connectivity measures was found in early multiple sclerosis patients. Given the relevance of well-validated scores to measure disability in the clinical follow-up of MS the correlation among those scales and resting state connectivity has been studied. The disability level as measured by the Multiple Sclerosis Functional Composite Score values were negatively correlated with increased connectivity within the dorsal frontoparietal network, the right ventral frontoparietal network and the prefrontal-insular network [60]. Also, connectivity has reported being shifted toward the DMN in cognitively less-efficient participants (anticorrelation), whereas it was shifted toward the control network in cognitively efficient participants (positive correlation) [61]. This evidence shows that it is possible to identify resting state change patterns with both an adaptive and maladaptive role in cognitive functioning.

Considering that clinical and anatomic features exhibit considerable variances between disease phenotypes, group differences in DMN activity were found in the left medial prefrontal cortex, left precentral gyrus, and anterior cingulate cortex, exhibiting different patterns for each group also related to cognitive performance [62]. That evidence must be interpreted as related to the role of spontaneous regional brain activity as an insight into the mechanisms underlying of behavioral impairment in MS [63].

When more subjective symptoms often reported in MS are studied under a rs-fMRI paradigm, interesting findings have also been reported. In sleep-disturbed patients, decreased functional connectivity between cognitively relevant areas as the thalamus, superior frontal gyrus, opercular cortex, cingulate, parietal cortex and precuneus have been shown, providing a neurodynamic explanation for some severe sleep disturbances in MS [64]. In the

Figure 4. Resting state networks. During mental rest, some brain areas exhibit correlated changes in their neural activity constituting well-differentiated functional units (here some examples). a) Default mode network: medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC) and lateral parietal (LP); b) Dorsal attentional network: frontal eye fields (FEF), inferior parietal sulcus (IPS); c) Language network: inferior frontal gyrus (IFG), posterior superior temporal gyrus; d) Salience network: rostral prefrontal cortex (RPFC), anterior cingulate cortex (ACC), anterior insula (Ainsula) and supramarginal gyrus (SMG).



case of fatigue, neurodynamic properties of the insula, caudate [65] and motor and executive network are contributing to the occurrence of centrally produced and persistent fatigue while hippocampal functional connectivity has reported being strongly correlated with severity of depressive symptoms and disability levels [66].

Also, rs-fMRI has reported being a useful tool for monitoring the therapeutic response based on functional reorganization [67,68], proposing an interesting role in the follow-up of these patients.

Conclusions

fMRI has strongly contributed to understanding neural mechanism underlying motor, visual and cognitive alterations in MS. Today, neural plasticity is a well-documented phenomenon occurring after an inflammatory and demyelinating lesion in the central nervous system. Despite the initially adaptive role of both structural and neurodynamic compensations during the early stages of the diseases, its prognostic utility and the potential for predicting phenotypes and evolution ways still remain unresolved. We consider fMRI contributions will increase when local clinical teams involved in the management of MS patients consider fMRI as a permanent part of the follow up of patients. At the same time, correlating fMRI findings with clinical performance in standardized neuropsychological evaluations will provide interesting additional evidence both in MS and in other neurological and neuropsychiatric diseases.

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Imágenes de resonancia magnética funcional en el estudio de la esclerosis múltiple

Introducción. La esclerosis múltiple (EM), una enfermedad neuroinflamatoria y desmielinizante, modifica la conectividad normal entre las diferentes regiones del cerebro involucradas en funciones específicas. La resonancia magnética funcional (RMf), basada en cambios locales en el nivel de oxígeno como respuesta al aumento de la actividad neuronal, proporciona un enfoque a la conectividad neuronal y la dinámica cerebral que ofrece una visión general de la disfunción visual, motora y cognitiva y sus mecanismos.

Desarrollo. Se realizó una búsqueda avanzada en PubMed considerando los términos '*fMRI*', '*visual*', '*motor*', '*cognitive*' y '*multiple sclerosis*' incluidos en el título y el resumen. La búsqueda se centró en artículos originales disponibles en inglés, con énfasis en los útiles para comprender los cambios funcionales en la EM. Numerosos estudios han utilizado la RMf como una herramienta complementaria en el estudio de la EM y las alteraciones clínicamente relevantes de la afectación visual, motora y cognitiva. Desde las primeras etapas de la EM, la actividad local y la dinámica neural global parecen estar afectadas. Incluso cuando el desempeño funcional aún se conserva, surge un reclutamiento diferente de los recursos neuronales como respuesta compensatoria a la desconexión observada en la enfermedad.

Conclusiones. Los principales hallazgos de la RMf aplicada a la EM están fuertemente relacionados con la naturaleza desmielinizante de la enfermedad y proporcionan una visión adecuada de los mecanismos subyacentes a las alteraciones funcionales. La RMf también parece ser útil para estudiar la evolución de la enfermedad y la respuesta al tratamiento en la EM y otros trastornos.

Palabras clave. Enfermedad del sistema nervioso. Enfermedades neurodegenerativas. Esclerosis múltiple. Neuroimagen. Neuroimagen funcional. RMf.