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Functional MRI to study brain plasticity in clinical neurology

Abstract Functional magnetic resonance imaging (fMRI) is being widely used to study recovery of function in patients with several neurological conditions, including multiple sclerosis, stroke and Alzheimer's disease. The application of this MR technique has shown that plastic cortical changes do occur after central nervous system (CNS) injury of different aetiology, that such changes are related to the extent of CNS damage and that they can contribute in limiting the clinical consequences of brain damage. Conversely, the failure or exhaustion of the adaptive properties of the cerebral cortex might be among the factors responsible for the accumulation of 'fixed' neurological deficits. New studies aimed at investigating the effect of therapies devoted to promote brain plasticity are now warranted.

Key words fMRI • Multiple sclerosis • Stroke • Alzheimer's disease • Brain plasticity

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Introduction

It is now well established that spontaneous clinical recovery may occur after central nervous system (CNS) injury associated with different neurological conditions. Over the past decade, a large effort has been devoted to achieve a better understanding of the mechanisms responsible for such a recovery with the ultimate goal of developing new and more effective treatment strategies. In this context, neurophysiologic and neuroimaging studies have provided convincing evidence that the adult human cerebral cortex is capable of significant functional plasticity, which may be due to different substrates, such as an increased axonal expression of sodium channels, synaptic changes, increased recruitment of parallel existing pathways or "latent" connections, and reorganisation of distant sites.

Functional magnetic resonance imaging (fMRI) is a safe and non-invasive method, which is currently used for investigating brain plasticity in healthy and diseased subjects. In this review, we describe the main results obtained from the application of fMRI to the assessment of patients affected by multiple sclerosis (MS), stroke and Alzheimer's disease (AD).

Multiple sclerosis

In MS, fMRI is progressively improving our understanding of the mechanisms responsible for the recovery of function and, conversely, for those associated to the accumulation of irreversible disability [1]. In this context, fMRI-based studies are suggesting that the lack or paucity of the correlation between structural MRI metrics and the clinical manifestations of the disease [2] could be explained, at least partially, by the variable effectiveness of inter-patient reparative and recovery mechanisms.

An altered recruitment of regions normally devoted to the performance of a given task and/or the recruitment of addi-

tional areas that are not typically activated by healthy people for performing that given task have been described in patients with MS, independent of their clinical phenotype when investigating the visual, cognitive and motor systems. These functional changes have been related not only to the extent and severity of brain damage within and outside T2-visible lesions and to the involvement of specific brain structures, such as the corticospinal tracts, but also to the degree of cord and optic nerve involvement. In addition, it has also been suggested that an altered recruitment of specific brain regions might be associated to the appearance of clinical symptoms in MS, such as fatigue. Brain functional changes have been shown to be dynamic over time, not only after an acute relapse, but also in clinically stable patients. More recently, in patients at a very early stage of the disease, it has been shown that such changes might be useful to predict the evolution to definite MS and it has been postulated that dynamic changes of brain cortical activations might occur with the progression of the disease from the relapsing-remitting to the secondary progressive phase [3]. An increased recruitment of the cerebral networks might represent a first step of cortical reorganisation with the potential to maintain a normal level of function in the course of MS. The progressive failure of these mechanisms might, on the one hand, result in the activation of previously silent 'second-order' compensatory areas, and, on the other, contribute to the accumulation of irreversible disability.

Stroke

The application of fMRI for the assessment of patients affected by stroke has demonstrated the presence of plastic mechanisms with a variable extent and efficacy after focal damage, which may contribute to the preservation of function. Such brain functional changes have been observed not only following injury to the motor system [4], but also as a consequence of damage to the speech areas [5]. After motor system damage, changes of function are not restricted to motor structures adjacent to the side of injury, but involve also more distant motor structures, either in the same hemisphere where injury has occurred or in the opposite one. Longitudinal studies confirmed the findings of cross-sectional studies, showing over-recruitment of motor and non-motor areas in both hemispheres in the acute stage. In addition, they also documented dynamic changes in these structures. In particular, a common observation is that the over-recruitment tends to decrease over time. In contrast, some structures tend to develop a later overactivation. In stroke patients, recovery of function can be modified by post-injury experience, as suggested by the demonstration that restricting the use of unimpaired limb can have a beneficial effect on motor recovery. Natural history, training therapy and pharmacological studies indicate that better recovery of function is associated with redistribution of activations toward the affected hemisphere. Studies of speech production suggest that recovery depends on slowly evolving activation changes in the left hemisphere. In contrast, right hemisphere activation changes have been interpreted as an effect of transcallosal disinhibition, which do not reflect recovery because they occur early after stroke in areas homologous to the lesion, and do not appear to correlate with the degree of recovery. As shown in MS, several factors have been demonstrated to influence the final pattern of cortical activations and the clinical outcome in patients with stroke. These factors include the location of the infarct (worst recovery for corticospinal tract damage), the chronicity of the lesion and the age of the patients. All these variables should be taken into account when studying novel therapeutic strategies for treating motor and language impairment after stroke.

Alzheimer's disease

Neuroimaging techniques, including fMRI, are being extensively applied as a way of predicting the evolution of disease in patients with mild cognitive impairment (MCI). In AD, neuroimaging is also being explored as a marker of disease progression and, therefore, as a potential surrogate marker of the effectiveness of new therapies.

Similar to what has been observed in MS and stroke patients, fMRI studies in AD patients have shown an increased activation of several cortical areas, reflecting functional compensation for neuronal loss, during the performance of cognitive tasks [6]. However, with disease progression, a reduced activation of specific brain regions, including the hippocampus and regions located in the temporal and parietal lobes, has been described by some Authors. The main problem in the interpretation of the patterns of activations seen in AD patients in the advanced phases of the disease lies in the fact that they are markedly biased by the ability of the patients to perform adequately the paradigm.

Intriguingly, fMRI has been demonstrated to be sensitive to early stages of brain pathology in AD. In this perspective, a pioneering study in healthy subjects at risk of developing AD showed an altered pattern of cortical activation during a memory task in subjects that, one year after fMRI acquisition developed memory problems [7]. These results have been confirmed by other studies [6].

Preliminary evidence suggests that fMRI might be a valuable tool to test and monitor treatment efficacy in AD patients. After cholinesterase inhibitor treatment, increased attention in AD patients has been related to increased activation of specific brain areas [8]. Furthermore, the response to cholinergic challenge has been shown to be different between MCI and AD patients [9], probably reflecting a difference in the functional status of the cholinergic system between the two groups, which is in line with recent results showing a differential clinical response to cholinergic treatment in AD and MCI patients.

Conclusions

The extensive application of fMRI for the assessment of patients with different neurological conditions is markedly improving our understanding of the mechanisms responsible for the accumulation of fixed neurological deficits and irreversible disability. Adaptation to structural damage is an established property of the human brain. The study of different activation paradigms and the development of sophisticated analysis methods have indeed provided fundamental insights into the physiological steps of cortical adaptation in the diseased brain. Further studies are now warranted to define the effects of treatments thought to be able to enhance brain plasticity.

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