

## fMR Imaging for Evaluation of Brain Plasticity in MS

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Plasticity or brain reorganization means different things to different scientists, but most would agree with the following definition proposed by *Donoghue JP et al in 1995: "Any enduring change in cortical properties either morphological or functional"(1).*

Plastic changes occur at the level of the synapses, and are consequently reflected at the level of neural networks. Plasticity is defined as a change at the synaptic level that increases communication efficiency in neural networks. Change of the strength of synapses is regulated through molecular and cellular transformation. It is important to distinguish *functional* from *structural plasticity*. The former changes synaptic strength without changing the anatomical connectivity between neurons, whereas structural plasticity comprises changes in synapse numbers, axonal fiber densities, axonal and dendritic branching patterns, synaptic connectivity patterns, and even neuronal cell numbers. Functional reorganization may be mediated by various processes, such as cell renewal, remyelination, neuritis extension, new synapse formation, ion channel redistribution and cortical reorganization processes involving the main associative pathways(2). Synaptic rewiring is the retraction of a pre- or postsynaptic element from its target and the subsequent turnover of a different target in reach. It is considered a form of structural plasticity. Synaptic rewiring is probably the most important feature of structural plasticity as it adds further degree of freedom for changing synaptic connectivity(3).

It has been established that humans show considerable plastic brain changes during development. The developing human brain

possesses a superior capacity to reorganize after focal lesions. Evidence of reorganization following pre- and perinatally-acquired, unilateral brain lesions for motor, somatosensory, and language functions have been documented for a long time(4). In healthy adults, plasticity is characterized by a decrease of focal brain activity going along with an increased connectivity between the collaborating nets.

In the adult damaged brain reorganization occurs and it is referred as *reactive plasticity*. Recovery may involve unmasking of pre-existing, but latent, interhemispheric connections and modulation of synaptic efficacy by long-term potentiation (LTP) or long-term depression (LTD)(5). Brain functions may be localized in functionally segregated brain regions but are mainly represented in extended, connected, overlapping and highly parallel processing networks. In patients with lesions of the nervous system plasticity is the active or passive process of reorganizing connections and re-coordinating a network of areas while function is recovering. Reactive plasticity is not restricted to perilesional cortex but includes also the homologous contralateral cortex. Bilateral rewiring is caused by interhemispheric disinhibition and unmasking of pre-existing callosal connections(6). Recovery of function seems to imply the "reconnection" or the recoordination of a network of areas.

Early in the stage of multiple sclerosis the pathological lesions are often associated with only subtle clinical symptoms although conventional T2-weighted MR imaging shows considerable signal abnormalities(7). This paradox might be explained with various factors inherent to the disease, such as that some of the lesions may be "silent" because they are located in non-functional territories, the occurrence of spontaneous repair and remyelination processes in patients with inflammatory lesions, and ion channel redistribution mechanisms. In addition, the existence of reorganization mechanisms reflecting the plasticity of the adult human brain has been amply documented during the past few years(7-11). The plastic processes occurring in response to pathological lesions may reduce the functional consequences of these

lesions and thus prevent or reduce clinical symptoms. It was recently suggested, on the basis of recent fMR imaging studies, that cortical reorganization processes of this kind might slow down the gradual aggravation of the disease. While in the early stages of multiple sclerosis these compensatory mechanisms may largely mask the functional effects of morphological lesions, as the disease evolves reorganization mechanisms may no longer suffice to compensate for the increasing lesions, thus symptoms begin to show up. One potential practical application of these adaptive mechanisms occurring in multiple sclerosis patients could be the development of specific rehabilitation strategies, which could be used to enhance reactive plastic mechanisms in order to maintain compensatory functional skills.

However, a word of caution is mandatory. Functional magnetic resonance (fMR) imaging based on the blood oxygenation level-dependent (BOLD) effect is a widely used technique for the investigation of changes in local brain activity upon stimulation during execution of a task. The principle of measurement is based on the assumption that there is a strong coupling between changes in neural activity, metabolism, vascular response and oxygen extraction in the area under investigation. The BOLD effect should be interpreted as a reflection of neuronal signaling and not as a locus of increased energy utilization. A large body of evidence indicates that neural activity is closely related to CBF. However, *neurovascular coupling may be disrupted* in pathological conditions, such as multiple sclerosis, ischemic stroke, hypertension, gliomas and Alzheimer disease. BOLD signals could reflect the neural processing occurring within a brain area, rather than the output from or input to that area(12). Interpretation of fMR imaging results in patients with brain disorders must take into consideration that atypical cerebral blood oxygenation changes may occur and influence the BOLD response.

## **References**

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