Editorial: Brain Plasticity
Has It a Role in Reducing Disability Related to Demyelinating Disease?

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Abstract

Patients with multiple sclerosis (MS) and other demyelinating conditions often show improvement from disease-related neurologic deficits. A number of factors have been proposed as contributing to this recovery. One possible mechanism that has received limited attention in the past is cortical plasticity, a process of active remodeling by which surviving resources are reorganized to maximize clinical status. Pilot studies of brain mapping in patients with MS and myelitis suggest that several motor cortex regions are organized differently than in healthy controls. Further studies are needed to evaluate the role of cortical plasticity in reducing disability among patients with MS. If further evidence supports a role for cortical remodeling in recovery from MS attacks, then treatments targeting the processes underlying cortical plasticity, such as growth factors currently being evaluated in stroke models, may represent new therapeutic avenues for patients with demyelinating disease.

Multiple sclerosis (MS), myelitis, and other demyelinating syndromes are an important cause of disability in adults. However, brain damage that occurs early in the course of the disease sometimes causes little or no lasting disability. Furthermore, many studies have found that clinical disability is only modestly correlated with the brain lesion volume as revealed by magnetic resonance imaging (MRI).

Several explanations for these findings have been proposed. Some of the clinical variability may be related to differences in immunopathogenetic mechanisms, the specific site of demyelination, or behavioral adaptation. Other reasons may include limited sensitivity of the imaging methods, remyelination, and failure to image the entire neuraxis when assessing disease burden in the central nervous system.1-3

One possible explanation for the disparity between MRI lesion volume and clinical status is cortical plasticity. Cortical plasticity refers to changes in the distribution of cortical function as measured by cortical mapping methods.4 Researchers have found plasticity in a wide number of
nonprimate and primate species, including humans; throughout multiple sensory and motor systems; and in numerous healthy and diseased nervous systems. For example, a number of changes have been found in language, vision, and motor systems in patients who have recovered from stroke.5-8 Some of these changes occur near regions of cortical damage: Traversa and colleagues5 found increased representation of paretic finger muscles in the affected hemisphere of patients with ischemic stroke; the degree of enlargement was linearly related to the extent of clinical improvement.

Other changes have been found in the intact hemisphere (ie, contralateral to the site of infarction). For example, several groups have identified increased activation, relative to controls, in sensorimotor cortex of the nonstroke hemisphere during movements by the previously paretic hand.6-8 Studies of animals with experimental infarct suggest various cellular and molecular events that correlate with the observations made in human brain mapping studies.9,10 Thus, after a monophasic demyelinating disease, or at early stages of MS, the brain may reorganize in response to damage and thereby stave off disability.

There are reasons to suspect that cortical plasticity might be an important determinant of neurologic status early in MS and after a monophasic demyelinating disease. Also, increasing evidence emphasizes the role of axonal damage and brain atrophy in the genesis of long-term disability in patients with MS. Trapp and colleagues11 have described two stages of MS disability genesis.

In the early stage, brain atrophy increases without concurrent progression of disability. Trapp and colleagues suggest that during this stage, clinical status is maintained by compensatory brain mechanisms. Studies in patients with stroke6 and spinal cord injury12 support the notion that cortical reorganization after axonal damage is associated with reduced disability. In the late stage, further brain damage leads to progressive disability. Theoretically, augmenting the compensatory mechanisms might slow the progression of disability during this stage.

Few brain-mapping studies have included patients with demyelinating conditions. Several studies have described metabolic abnormalities in the brains of MS patients; and in some cases, the abnormalities correlated with the extent of clinical deficits or radiologic abnormalities.13-16 However, these studies were performed with patients at rest and therefore did not examine brain activation. Rombouts and colleagues17 used an 8-Hz stroboscopic stimulation during functional MRI (fMRI) to compare posterior brain activation volumes in control subjects with those in MS patients with a history of unilateral optic neuritis. Compared with controls, the MS patients showed decreased activation volumes during unilateral stimulation of either eye. Also, stimulation of the affected eye activated a smaller volume than did stimulation of the contralateral eye. Similar results were reported by Gareau and colleagues.18

Yousry and colleagues19 compared eight MS patients with eight controls. During a finger motor task, an undefined subset of patients showed motor cortex activation. In this brief report, the authors also noted that "with partial motor weakness, patients activated larger motor areas on both hemispheres," including bilateral motor cortex and the supplementary motor area.

A previous study20 used fMRI to measure cortical activation during a finger-tapping task to evaluate motor cortex reorganization in patients with myelitis. Seven patients who had measurable recovery from hand motor deficits after myelitis involving the cervical cord and who had no diagnosis of MS were compared with nine healthy controls. The patients’ median Expanded Disability Status Scale (EDSS) score was 2.0. Compared with controls, the myelitis patients had a greater volume of cortical activation, particularly in contralateral sensorimotor cortex and premotor cortex. For the myelitis patients, the degree of daily hand use was positively correlated with the activation volume in the contralateral sensorimotor cortex. Thus,
enlarged activation volume within the contralateral sensorimotor and premotor cortices may represent an adaptive response for maximizing motor outcome.

Lee and colleagues evaluated motor cortex activation during finger movements in patients with clinically stable MS (mean EDSS score, 6.5) and in control subjects. There were few between-group differences in brain activation. Unlike in the myelitis study, however, the degree of functional impairment among MS patients was inversely related to the activation volume in the contralateral sensorimotor cortex. Contralateral motor cortex activation was shifted posteriorly by an average of 9 mm; the amount of shift was positively correlated with the MS lesion burden in the hemisphere. Also, recruitment of sensorimotor cortex ipsilateral to the tapping fingers increased as lesion burden increased. A posterior shift in motor cortex activation and increased activation of motor cortex ipsilateral to the active hand have also been found in patients with good recovery from stroke, thus supporting the idea that there is overlap in restorative events between stroke and MS.

Further studies exploring the extent and significance of cortical plasticity in patients with MS may serve several purposes. They should help establish links between several observed clinical manifestations. First, variation in plasticity may explain some of the heterogeneity seen in clinical outcomes in MS patients, such as the relationship between the volume of brain abnormalities on T2-weighted MRI and disability. Second, establishing the presence and timing of cortical plasticity may clarify the role of physiotherapy in reducing disability in MS patients. For example, after spinal cord injury and infarct, intense physiotherapy may interact with cortical plasticity to improve clinical outcome. Third, establishing an overlap between the cortical plasticity events found in patients with MS and those found in stroke patients may suggest novel therapeutic approaches to MS. In animal models of stroke, for example, administration of growth factors that target the cellular processes underlying plasticity has been associated with improved clinical outcome. Brain mapping studies in humans may suggest the need for animal studies that evaluate these growth factors in animal models of demyelinating disease.

Finally, understanding how cortical reorganization relates to total lesion burden will be important. Cramer and colleagues found that enlarged activation volume in the contralateral sensorimotor cortex was associated with better motor status in patients with mild residual disability, while Lee and colleagues found that enlarged activation in the contralateral sensorimotor cortex was associated with poorer motor status. Thus, the significance of cortical plasticity in patients with mild, moderate, or severe MS remains unclear.

Even though several new treatments for MS have been introduced in recent years, MS remains a major cause of disability. Like so many other processes that damage the nervous system, demyelinating disease—which is known to be associated with axonal damage—may be associated with compensatory responses in the brain. Understanding these responses—their nature, frequency, distribution, and clinical significance—may provide insights into brain events that help determine the level of disability in patients with MS. Further studies exploring the brain reorganization in MS patients may lay the groundwork for trials of therapies that target brain reorganization.

References


