The virtues of adaptability

The recognition that acute inflammatory events are associated with irreversible axonal loss and that axonal and neuronal loss is extensive brought new conundrums for multiple sclerosis (MS) researchers.1,2 How does functional recovery occur after relapses when axons are lost? How can people with MS show normal levels of behaviour and performance despite significant neurodegeneration? Demonstration of abnormal patterns of brain activation associated with unimpaired task performance in people with MS provided indirect evidence that central nervous system (CNS) adaptive plasticity could provide a partial answer to both questions.3 Multiple mechanisms likely contribute to plasticity, including synaptic remodelling, remyelination, new neurite growth and neuronal regeneration.4 In rare instances, the spontaneous evolution of adaptive plasticity with recovery from an acute relapse has been documented.5 Nonetheless, over the longer term, the cumulative loss of synaptic density and neurons might be expected to limit adaptive plasticity related to remodelling, growth and regeneration.6 This could be a proximate mechanism responsible for incomplete functional recovery after an acute relapse or the progression of disability. However, direct evidence in support of this hypothesis has been hard to elicit. In fact the observation of preserved motor learning even in people with MS who have substantial disability appears to provide evidence to refute the hypothesis.7

In this issue of Multiple Sclerosis Journal, Mori and colleagues have begun to re-address this issue with an elegant set of non-invasive electrophysiological studies in people with MS with low disability, recruited within a day of an acute relapse.8 Their primary test used paired associated stimuli (PAS) as a probe for short-term motor cortical plasticity. The technique relies on strengthening of synaptic strength with simultaneous reinforcing of neuronal inputs. It is performed by coupling both delivery of volleys with afferent electrical stimulation of the median nerve and stimulation of efferent cortical motor neurons by transcranial magnetic stimulation. This repeated, simultaneous sensory and motor nerve stimulation transiently augments the size of individual motor evoked potentials (MEPs) induced for the abductor pollicis brevis (APB). The magnitude of the augmentation provides a precise, reproducible measure of short-term motor cortical plasticity which can be interpreted as reflecting phenomena similar to the long-term potentiation (LTP) defined preclinically.9 Mori et al. analysed their results by dividing their subjects into those who showed complete, partial or little recovery within 12 weeks of a relapse.8 Those who later had a complete recovery showed an augmentation of their responses consistent with the expected LTP-like effect. By contrast, subjects who had incomplete or little recovery showed a relative suppression of their APB MEP, showing a phenomenon similar to long-term depression (LTD), the stimulus-induced depression of synaptic plasticity.9 In the small population studied, age and the magnitude of the PAS response together explained almost half ($r^2=0.39$) of the subsequent motor recovery.

The authors suggest that the extent of acute impairment of motor cortical plasticity determines the potential for subsequent adaptive plasticity. Intuitively, this is an attractive concept. A related study in patients after their first motor stroke demonstrated increased excitability of the affected motor cortex in patients with good recovery and came to a similar conclusion in that context.10 Multiple factors may be involved. For example, because the motor cortices in the two hemispheres mutually inhibit each other during unilateral limb movements, the integrity of the contralateral motor cortex and associated transcallosal inhibitory pathways is one determinant of the excitability and short-term plasticity of the affected motor cortex.10,11 In addition to direct neurodegenerative effects, multiple inflammatory effectors, including interleukin (IL)-1β, tumour necrosis factor (TNF)α, interferon γ and nitric oxide, can inhibit plasticity.12 Mori et al. also found that age was correlated negatively with recovery.8 LTP declines with age in healthy volunteers13 and may contribute to the age-related effects reported here in people with MS. However, the influence of age also could reflect interactions between age and neurodegeneration during the acute relapse that were not controlled in the study.14 Aging is also associated with reduced capacity for remyelination15 and neuro-regeneration.16 Whatever the mechanism, the data presented imply that mechanisms independent of those associated solely with short-term plasticity make a contribution to recovery at 12 weeks.
What are the implications of this work? The most obvious conclusion is that inflammatory activity or its short-term consequences impair local mechanisms responsible for both short-term plasticity (as measured) and the longer-term motor plasticity reflected in the 12-week clinical outcomes. This suggests that suppression of this inflammatory activity could limit relapses, decrease the clinical severity of relapses and enhance the rate of recovery from them, as well as decreasing relapse-related disability progression. It highlights the difficulty of disentangling the effects of medicines that suppress inflammation from those promoting recovery or plasticity. Developing improved measures for sensitive, dynamic monitoring of impairment and disability could allow better differentiation of medicines on the basis of plasticity-related outcomes. If so, this would provide a powerful set of tools for demonstrating the value of combining an anti-inflammatory approach with molecules that promote plasticity. Remyelinating agents are an obvious candidate approach for the latter, but the line of thought also suggests a much broader range of targets. For example, a novel, 'druggable' mechanism potentially contributing to inflammation—associated impairment of LTP-like phenomenon is IL-1β inhibition of brain-derived neurotrophic factor (BDNF) signalling through the TrkB receptor via the p38 mitogen-activated protein kinase (MAPK).17

How can the results reported here be reconciled with the lack of impairment of longer-term plasticity associated with chronic motor training described earlier?17 One possibility is that low-grade, chronic inflammation has two opposing classes of effects. While it antagonises BDNF-mediated plasticity, with effects on glial cells to increase glutamate and promote degeneration of interneurons, it may decrease the neural excitation threshold to maintain normal levels of adaptation.18 If so, this would represent another manifestation of the 'Janus face' of inflammation in MS, whereby chronic brain inflammation has both neurodegenerative and reparative consequences.

Like all good experiments, the one reported by Mori et al.8 raises more questions than it answers! Do outcomes at 12 weeks predict those over a longer period? Is the time course of the acute inflammatory response and enhanced local cytokine release correlated with the magnitude of impairments of LTP-like responses? Does acute steroid treatment rapidly reverse these effects in ways that could suggest potential for longer-term benefits? Are current medicines or molecules in development able to modulate the relationship between any acute inflammation-related impairment of plasticity and longer-term outcomes?

Mori and colleagues demonstrate well the value of careful, physiological assessments for understanding MS.8 These results highlight the importance of exploring CNS plasticity in the context of MS and the intriguing potential that its direct modulation through electrophysiological or pharmacological mechanisms might bring.

Conflict of interest
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References


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