MOTOR SYSTEM PLASTICITY AND COMPENSATION IN MULTIPLE SCLEROSIS

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ABSTRACT

Multiple sclerosis (MS) affects the central nervous system (CNS) by inflammatory lesions, direct axonal injury, and by a rather diffuse and widespread neurodegeneration. For a long time, research has mainly focused on these destructive aspects of MS, while the compensatory effects of cellular repair and neural plasticity have received little consideration. However, as current effective immunomodulatory therapies may limit rather than preclude demyelination and axonal damage, additional therapeutic strategies promoting compensation of CNS damage might be of great use for preventing persistent impairment in MS. As a precondition for the development of such strategies, which may encompass pharmacological and behavioural interventions, but also non-invasive stimulation techniques, it seems fundamental to get deeper insights into the mechanisms of plasticity and adaptation at the systemic level. This review will provide a brief overview of what is known about plasticity of the motor system in patients with MS at present, with the main focus relying on evidence from functional imaging, neurophysiology, and motor learning. Overall, rapid-onset motor plasticity seems to be preserved even in advanced stages of the disease. Reorganisation processes, which can be shown early in the course of MS, are functionally relevant for motor compensation. In advanced MS, however, the brain´s adaptive reserve might be exhausted due to exceeding CNS injury. Future studies should address the question of how the later stages of central motor plasticity can be promoted best to preserve the patient´s autonomy for as long as possible.

Keywords: Multiple sclerosis, plasticity, motor system, adaptation, reorganisation, compensation, functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS).

CLINICAL EVIDENCE OF ADAPTATION IN MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an immune-mediated disease that is characterised by inflammation and neurodegeneration within the central nervous system (CNS).[1] While the most characteristic pathological change in MS is the formation of large confluent demyelinated plaques in the white matter of the brain, cortical lesions are also present in early stages of MS.[1] In the majority of patients, MS initially shows a relapsing-remitting course (RRMS) with episodes of neurological impairment that occur months or years apart and affect different functional systems. As revealed by longitudinal studies, these episodes should be viewed as the tip of the iceberg since, on average, only about 5-20% of new lesions detectable on brain magnetic resonance imaging (MRI) are associated with clinical symptoms or signs.[2] Accordingly, the so-called 'clinico-radiological paradox' of MS refers to the common discrepancy between pathological findings on brain MRI on the one hand and clinical symptoms on the other.[3] This discrepancy can be particularly impressive in a subgroup of patients suffering from a clinically 'benign' phenotype of RRMS with preserved functional capacity for years in spite of a high CNS lesion load.[4]

Altogether, since repair on the cellular level commonly remains incomplete,[5-7] there must be additional mechanisms accounting for recovery from or nonappearance of symptoms despite persistent structural damage. Commonly, these

kinds of adaptive changes are attributed to neural plasticity, which refers to the capacity of single neurons or neuronal systems to adapt dynamically in response to external stimuli, environmental changes, or lesions.[8] In this context, the term 'plasticity' summarises a number of mechanisms which may operate on a timescale from minutes to months (Figure 1) and which seem to occur partly in parallel, partly successively.[9] Unmasking of latent neuronal connections[10] or increasing neuronal membrane excitability by altering the expression of ion channels[11] can be quick ways of adaptation. At the synaptic level, synaptic efficacy can be modulated in terms of long-term potentiation (LTP) or long-term depression (LTD).[12,13] Moreover, metaplastic phenomena might promote efficient recovery.[14] In contrast to these rapid-onset mechanisms, the anatomical changes underlying chronic cortical reorganisation might require the formation of new synapses and sprouting of axons to form compensatory pathways[15] and hence take more time (Figure 1). But are the mechanisms underlying rapid-onset neural plasticity and chronic reorganisation available in MS in spite of the whole-brain pathology, especially in view of the cortical involvement which may critically interfere with those mechanisms? Are they functionally relevant for the compensation of MS-related CNS injury at all? These questions will be assessed below based on data from functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), and motor training studies.

RAPID-ONSET CENTRAL MOTOR PLASTICITY

Rapid-onset central motor plasticity may occur on a timescale of minutes to hours (Figure 1, left box). The question of whether this early type of motor plasticity is preserved in patients with RRMS is of great interest. If we suppose that rapid-onset processes represent initial steps of more slowly evolving mechanisms of motor plasticity,[16] they might be rate-limiting on the course to successful adaptive reorganisation (Figure 1). Rapid-onset plasticity can be induced exogenously by non-invasive stimulation techniques such as TMS or transcranial direct current stimulation (tDCS), or endogenously by motor training tasks.[17-19]

Stimulation-Induced Plasticity

We have previously studied rapid-onset central motor plasticity and its relationship to motor impairment and CNS injury in patients with stable MS (RRMS or secondary progressive MS [SPMS], no relapse, and no changes of disease modifying treatment [DMT] within 3 months).[20] Paired associative stimulation (PAS), a protocol combining electric nerve stimulation with TMS of the contralateral motor cortex, may induce Hebbian LTP of synaptic efficacy in the human motor cortex.[21,22] PAS-induced plasticity shares distinct physiologic properties with synaptic LTP,[20-22] which is tightly related to skill acquisition in a motor training task.[20,23]

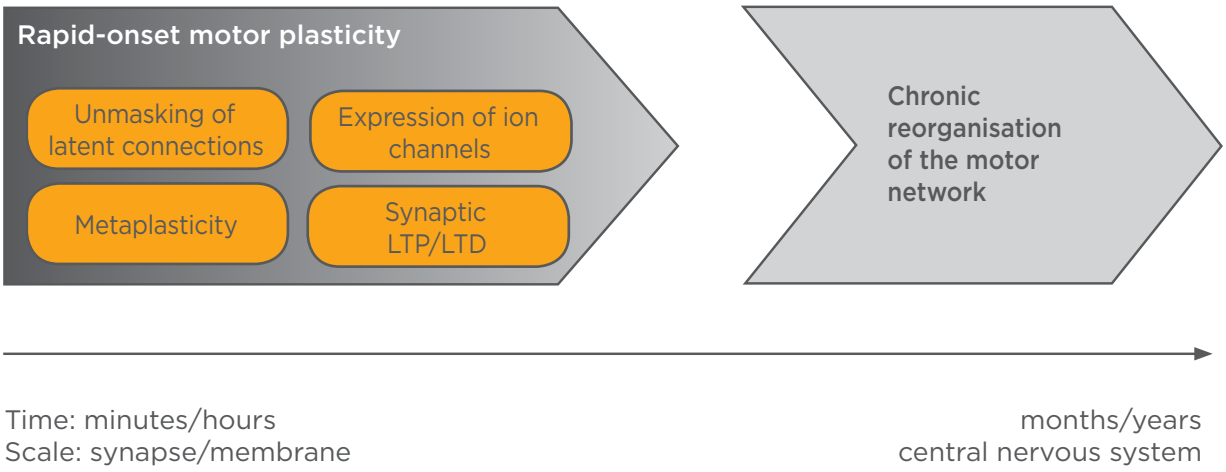

Figure 1: Depending on the spatial and temporal scales considered, a number of mechanisms may contribute to neural plasticity, reorganisation, and adaptation of the motor system. Rapid-onset processes (left box) are believed to represent initial steps of more slowly evolving mechanisms of motor plasticity and chronic reorganisation (right box).
LTD: long-term depression; LTP: long-term potentiation.

We found the PAS-induced enhancement of corticospinal excitability to be comparable between patients with moderately severe MS and matched controls.[20] There was no correlation between the changes of corticospinal excitability and the impairment of hand function or measures of CNS injury. PAS-induced plasticity in patients with high CNS injury and good motor performance was similar to the plasticity in patients with high CNS injury and poor motor performance. Thus, in spite of motor impairment and CNS injury, LTP-like rapid-onset motor plasticity in MS patients was comparable to that in healthy subjects.[20] As compensation of MS-related brain injury might also require excitability-decreasing mechanisms to focus on neuronal activity facilitating recovery of a specific motor function, we also assessed LTD-like rapid-onset motor plasticity in patients with RRMS (stable for ≥3 months). We applied an excitability-decreasing TMS protocol (continuous theta-burst stimulation [cTBS][24]), consisting of high-frequency, low-intensity bursts of three pulses, over the primary motor cortex (M1).[25] cTBS induces a depression of corticospinal excitability whose physiological properties are similar to those observed for LTD as studied in animal preparations.[24,26,27] Motor-evoked potential amplitudes were comparably reduced by cTBS in MS patients and matched controls. Altogether, LTP and LTD-like 'exogenous' motor plasticity remains largely intact in patients with mild-to-moderate MS. Therefore, compensation of MS-related CNS injury is unlikely to be constrained by insufficient rapid-onset neuroplasticity.

During a relapse of MS, PAS-induced LTP-like plasticity has been demonstrated to be normal in patients with complete recovery from the relapse 12 weeks after, but impaired in patients with incomplete or absent recovery.[28] This suggests that synaptic plasticity contributes to symptom recovery after a relapse, and that PAS effects may predict recovery from a relapse.[28]

Several pharmacological and biochemical factors have been shown to influence rapid-onset plasticity. For example, exposure of MS patients to a cannabis-based preparation used in the treatment of spasticity resulted in a shift in the polarity of synaptic plasticity induced by cTBS, pointing to metaplastic effects of cannabis ingredients on the motor cortex in MS patients.[29] Moreover, contents of amyloid-β_{1-42} in the cerebrospinal fluid (CSF) correlated with cortical plasticity deficits in MS, probably indicating that central inflammation due to MS is able to alter amyloid-β metabolism, leading to impairment of synaptic plasticity.[30] Platelet-derived growth factor in the CSF might play a role in favouring the brain plasticity reserve, which is believed to be crucial to contrast clinical deterioration in MS.[31] In addition, early application of disease modifying drugs may prove beneficial by reversing cognitive and cortical plasticity deficits in MS.[32] Finally, the subtype of MS was shown to influence the expression of stimulation-induced LTP-like motor plasticity in MS patients.[31]

Training-Induced Plasticity

Aside from exogenous stimulation protocols, motor plasticity can be induced by repeated performance of a motor task. Motor learning may challenge rapid-onset mechanisms of central motor plasticity and may result in a reorganisation of the output organisation of the motor cortex.[33,34] We tested motor learning in the course of repeated runs of a force production task and found comparable training-induced improvements of motor performance in MS patients without a relapse for at least 3 months and controls.[20] Motor learning performance did not correlate with motor impairment or measures of CNS injury, and was not different between patients with high CNS injury and good motor performance and those with high CNS injury and poor motor performance.[20] In line with these results, Tomassini et al.[35] reported comparable increments in short and long-term motor learning in MS patients (RRMS and SPMS) and matched controls. Even the patients with the most severe CNS damage showed a comparable success in the course of motor training.[35]

In a subsequent study[36] by the same group, behavioural and fMRI data were assessed during short-term (first practice session) and longer-term (after 2 weeks of daily practice) training of a visuomotor task. Again, MS patients and controls showed comparable performance improvements independent of MS-related brain pathology in MS patients.[36] However, brain regions relevant for improvements of the visuomotor performance differed between patients and controls: greater short-term improvements were associated with lower activation in the sensorimotor, posterior cingulate, and parahippocampal cortices for MS patients, whereas greater long-term improvements correlated with smaller activation reductions in the visual cortex of controls.[36] Hence, brain plasticity for visuomotor practice may be preserved in MS

patients, but partly based on systems different from those acting in healthy controls.[36]

CHRONIC REORGANISATION

Adaptive (and probably also maladaptive) reorganisation in response to MS-related CNS injury is described at the motor system level of the brain and may occur months to years after brain injury (see Figure 1, right box). It can be assessed by fMRI and by non-invasive stimulation methods. While fMRI provides a large-scale average of brain activity by detecting changes in local blood flow, stimulation techniques like TMS can probe the functional role of cortical reorganisation by inducing 'virtual lesions'.

fMRI

The majority of fMRI studies have investigated evidence for reorganisation of the motor system during the remitting (relapse-free) phase of MS. An important study by Reddy et al.[37] demonstrated that cortical adaptive responses contribute to the maintenance of normal motor function in MS patients with unimpaired hand function despite magnetic resonance (MR)-spectroscopic evidence of diffuse axonal injury. In MS patients, the activation of the ipsilateral sensorimotor cortex (SMC) with simple hand movements was increased as compared to controls, and the extent of this increase was strongly correlated with axonal injury as indicated by MR spectroscopy. These results point to an important role of cortical adaptive responses in compensating for axonal injury, even at the subclinical level of MS.[37] Taken together with subsequent studies based on fMRI during a motor task,[38,39] MS patients may need to activate more widespread sensorimotor networks to achieve a similar hand function as compared to healthy volunteers.[37-39] The association of additional activation with the extent of brain damage[37-40] suggests a compensatory function of such activation, which may develop over time in response to a functional demand.[39]

As fMRI changes can also occur due to disability, Reddy and colleagues[41] used an active as well as a passive finger movement task to test whether (at least part of) the fMRI changes were independent from voluntary recruitment and, thus, likely to reflect true functional reorganisation. MS patients were stratified according to diffuse brain injury (DBI) as assessed from MR spectroscopy (N-acetylaspartate concentration) and hand function.[41] Increased activity in ipsilateral sensorimotor networks correlated highly between active and passive finger movements. Patients matched for DBI, but differing in hand disability, showed greater bilateral primary and secondary somatosensory cortex activation with greater disability. Patients matched for hand disability, but differing in DBI, showed increased ipsilateral premotor cortex and bilateral supplementary motor area (SMA) activity with greater DBI. Changes of brain activation related to disability may, therefore, reflect responses to altered patterns of use, while those related to injury and disability - and even detectable with passive finger movements - may reflect true brain reorganisation.[41]

While longitudinal studies of plasticity in MS patients over the course of years are lacking, the temporal evolution of cortical reorganisation was studied by comparing patients with clinically isolated syndrome (CIS), RRMS, and SPMS.[42] During fMRI, MS patients performed a simple motor task with the unimpaired dominant hand. Early in the disease course (CIS) more areas typically devoted to motor tasks were recruited, then bilateral activation of these regions was seen, and late in the disease course (SPMS), areas that healthy people recruit to do novel or complex tasks were activated.[42] Hence, cortical reorganisation seems to vary across different stages of MS. However, there can be remarkable differences with respect to the disease course: a subgroup of patients presents with so-called benign MS (BMS), which is defined by an Expanded Disability Status Scale (EDSS) score ≤3.0 and a disease duration ≥15 years. Given a comparable lesion burden, patients with BMS differed from those with a SPMS phenotype with respect to movement-associated brain activations in fMRI: patients with SPMS showed increased activations of the occipital and left secondary SMC, inferior frontal gyrus, and right hippocampus, whereas they had reduced activations of the left SMA, putamen, and right cerebellum as compared to patients with BMS or healthy controls.[43] The rather selective and lateralised pattern found in patients with BMS largely resembled that of healthy controls.[43] Therefore, a functional adaptive reserve of the brain which is preserved over the long term is likely to contribute to a favourable clinical course of MS.[43]

In addition to sensorimotor cortical areas, the cerebellum is likely to contribute to motor compensation. Saini et al.[44] have assessed

neocortical–cerebellar functional connectivity by fMRI based on correlations between signal intensity changes in selected neocortical and cerebellar regions of interest. Subjects were asked to write '8' repeatedly on paper with a pencil in their right hand to complete one figure every second.[44] While healthy controls showed strong functional connectivity between the left motor cortex and the right cerebellar dentate nucleus, RRMS patients (EDSS ≤2.5, relapse-free for at least 3 months) had significant connectivity between the left premotor neocortex and the ipsilateral (left) cerebellar cortex, which was not found in the control group. Similar connectivity changes have been reported in the healthy brain during motor learning, suggesting that common mechanisms may contribute to normal motor learning and motor compensation after MS-related brain injury.[44]

Only a few studies have addressed brain reorganisation during an acute relapse of RRMS. In a case study of one patient, Reddy and colleagues[45] reported serial MR spectroscopy and functional MRI after new onset of hemiparesis from a relapse of MS. Clinical improvement was accompanied by recovery of neutron activation analysis (NAA), a MR-spectroscopic marker of neuronal integrity, and by a gradual reduction of abnormally large fMRI cortical activation with movement, demonstrating that dynamic reorganisation of the motor cortex may accompany remission from a relapse.[45] Following an acute relapse involving the motor system, Mezzapesa and colleagues[46] assessed cortical reorganisation over time by fMRI during performance of a simple motor task. At baseline, the primary SMC of the contralesional hemisphere was more active during task performance with the impaired as compared to the unimpaired hand. A recovery of function of the primary SMC of the affected hemisphere was associated with clinical improvement, while patients without clinical recovery persistently recruited the primary SMC of the unaffected hemisphere. Thus, the regain of function of motor areas of the affected hemisphere seems to be crucial for a favourable recovery from a relapse.[46]

TMS-Induced Virtual Lesions

We have previously studied the role of two ipsilateral motor areas during performance of a simple reaction time (RT) task in patients with stable MS in relation to their motor impairment and CNS injury.[47] Subjects responded to a Go signal as quickly as possible by performing isometric right-thumb abduction. To interfere transiently with neuronal processing, we used single pulses of TMS over contralateral ($M1_{contra}$) or ipsilateral ($M1_{ipsi}$) primary motor cortex or ipsilateral dorsal premotor cortex (PMd_{ipsi}). Motor impairment was evaluated by hand function tests. CNS injury was assessed by MR spectroscopy (relative NAA concentration), by the total cerebral tesla-2-weighted MRI hyperintense lesion load, and by the corticomuscular latency (CML) to the abductor pollicis brevis muscle. TMS over $M1_{contra}$ slowed RT in patients and controls, whereas stimulation of $M1_{ipsi}$ or PMd_{ipsi} increased RT only in MS patients.[47] Hence, recruitment of ipsilateral motor areas during a simple RT task may be functionally relevant in MS patients, but not in healthy subjects. Remarkably, there was a negative correlation between RT changes following TMS over $M1_{ipsi}$ and CML in MS patients. In other words, an increasing affection of the corticospinal tract to the dominant hand was associated with a less prolonged RT after TMS over the ipsilateral M1; importantly, this effect was not due to differences in baseline performance between MS patients. Taken together, these results may point to an important difference between MS and diseases with focal pathology: as the MS pathology also affects compensating brain regions, the capacity of the ipsilateral M1 to compensate dysfunction of the contralateral corticospinal tract may decrease (even though assumedly starting from variable levels) with higher regional injury.[47]

To probe the functional role of the contralateral M1 in force control in patients with stable RRMS as compared to matched controls, we assessed force production performance (FPP) in an isometric right thumb abduction task before and immediately after cTBS[24] over M1.[25] cTBS impaired FPP significantly in controls, but not in MS patients. However, FPP changes following cTBS correlated with CML in MS patients. Thus, increasing brain injury may render the neuronal networks less responsive toward lesion-induction by cTBS.[25]

CONCLUSION

Current evidence suggests that rapid-onset motor plasticity is preserved even in advanced stages of MS. Chronic reorganisation can be demonstrated early in the disease course and is functionally relevant to maintain motor function.

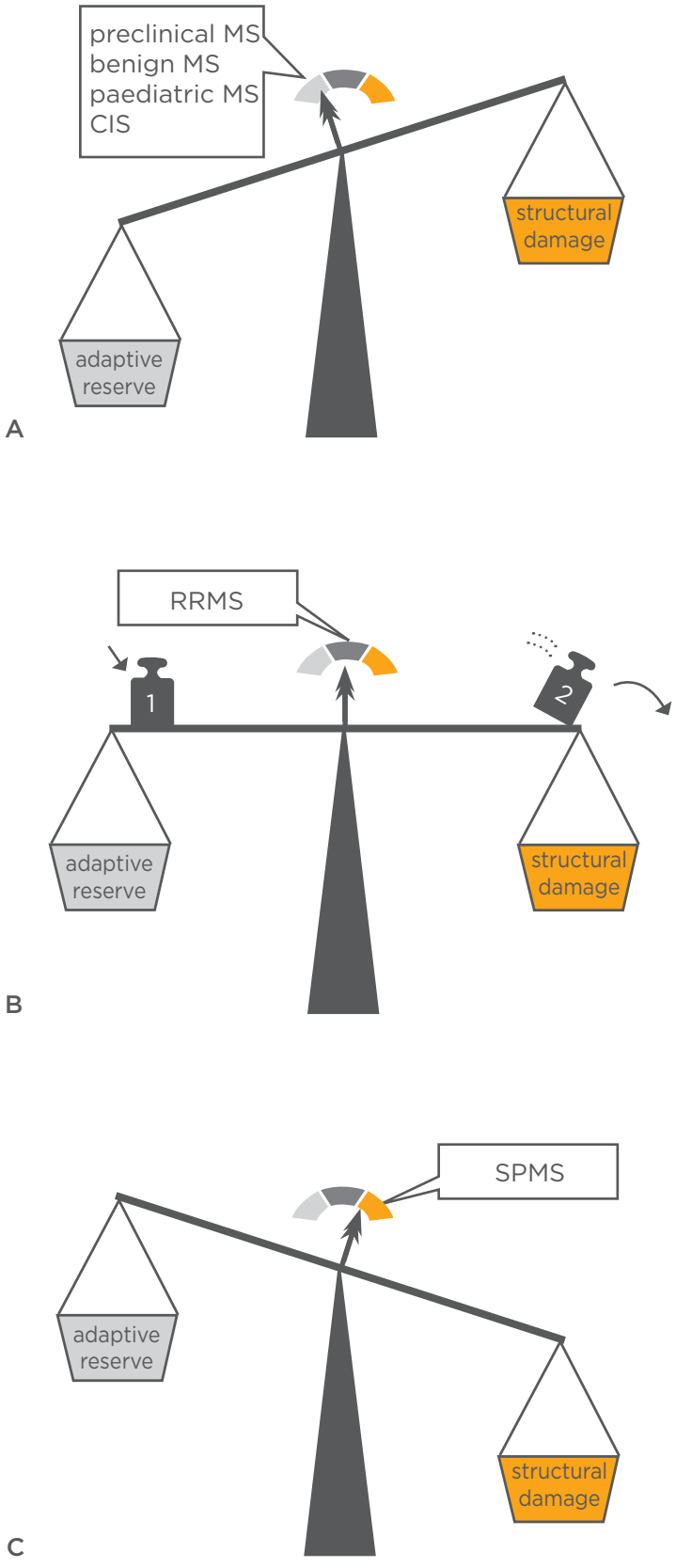

Figure 2: Schematic simplified illustration of the interaction between the adaptive reserve of the brain and MS-related structural CNS damage: A) early MS or benign courses of MS; B) relapsing-remitting phase with damage and compensation balancing each other (weights indicate therapeutic targets: 1) promotion of beneficial neural plasticity; 2) prevention of CNS damage); C) advanced MS.

CNS: central nervous system; CIS: clinically isolated syndrome; MS: multiple sclerosis; RRMS; relapsing-remitting MS; SPMS: secondary progressive MS.

Compared to healthy people, MS patients may need to activate more widespread sensorimotor networks to achieve a similar hand function. The extent of additional activation correlates with the extent of global and focal brain damage, suggesting a compensatory role of this adaptation. Accordingly, activation patterns close to normal can be found in early stages of MS, favourable clinical courses of MS, and during the remitting phase of MS. Therefore, the preservation of the brain´s functional adaptive reserve, which seems to be limited by high CNS injury in advanced stages of the disease, might constitute one of the main factors determining the clinical course of MS over the long term (Figure 2A-C).

In addition to established disease modifying and immunosuppressive treatments which are aimed at preventing CNS damage (Figure 2B, weight 2), future therapies might target the promotion of the brain´s innate ability to compensate for MS-related dysfunction (Figure 2B, weight 1). This may involve pharmacological and behavioural approaches as well as non-invasive stimulation techniques such as tDCS, which has already shown promising preliminary results in other neurological diseases (reviewed in[19]). In respect of rehabilitation, efforts may need to focus on mechanisms promoting the later stages of central motor plasticity, since short-term plasticity is largely preserved and, thus, may not represent a promising therapeutic target. To address the question of which rehabilitation approaches most efficiently induce endogenous plasticity, high-quality studies probing the effects of standardised training interventions on fMRI or TMS measures of plasticity in well-defined groups of MS patients are needed.

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