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Neuroplasticity and functional recovery in multiple sclerosis

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Abstract

The development of therapeutic strategies that promote functional recovery is a major goal of multiple sclerosis (MS) research. Neuroscientific and methodological advances have improved our understanding of the brain's recovery from damage, generating novel hypotheses for potential targets or modes of intervention and laying the foundation for the development of scientifically informed strategies promoting recovery in interventional studies. This Review aims to encourage the transition from characterization of recovery mechanisms to the development of strategies that promote recovery in MS. We discuss current evidence for functional reorganization that underlies recovery and its implications for development of new recovery-oriented strategies in MS.

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Promotion of functional recovery requires an improved understanding of recovery mechanisms modulated by interventions and the development of reliable measures of therapeutic effects. As imaging methods can be used to measure functional and structural alterations associated with recovery, this Review discusses their use as reliable markers to measure the effects of interventions.

Introduction

Inflammatory demyelination and axonal loss are considered major determinants of neurological deficits in Multiple Sclerosis (MS)[1]. Functional recovery in MS is achieved and sustained by repair of damage through remyelination with resolution of inflammation and functional reorganisation. *Remyelination* is an important mechanism of restoration of axonal function after acute inflammatory demyelination[2]. *Functional reorganisation* relies on molecular and cellular mechanisms to induce changes in systems-level functional responses, which are the proximal effectors of perception, action and cognition. This review focuses on systems-level adaptive functional reorganisation in MS as measured by functional MRI (fMRI), discussing mechanisms of functional recovery and ways to enhance them.

The overall aim of this Review is to stimulate progress from studies characterising recovery mechanisms to studies developing strategies to promote recovery in MS. In the first section, we summarize evidence from imaging studies that shows adaptation of functional systems to damage to emphasise principles of adaptive functional reorganization. In the second section, we propose ways in which this understanding can be translated into new recovery-oriented strategies for MS, supported by related findings in other neurological conditions. As our understanding of recovery mechanisms and the development of interventions are influenced by our ability to measure the desired effects, the third section discusses the opportunities and limitations of imaging methods that are used to measure neuroplasticity underlying functional recovery in order to improve their application as reliable and quantitative measures of therapeutic interventions[3,4]. This will extend opportunities for neurorepair to other disabling neurological conditions.

Adaptive functional reorganization in MS

Evidence for reorganisation of brain function underlying functional recovery comes from studies of focal ischaemic brain damage, where systems-level reorganisation reflects molecular, synaptic and cellular events and constitutes post-injury *brain plasticity*[5,6]. Perilesional remapping of cortical representations, functional reorganisation in intact regions of the damaged hemisphere and activation of cortical areas in the undamaged hemisphere accompany functional recovery after stroke[5]. Several lines of evidence show that such reorganization is behaviourally relevant for stroke recovery as **(a)** it is associated with preserved or completely recovered behaviour[7]; **(b)** the extent of functional changes correlates with the associated pathology[8]; **(c)** similar changes can be induced through learning or rehabilitation[9]; **(d)** potential for recovery increases with facilitated reorganization[9]; **(e)** functional impairment results from interference with such processes[10] (Box 1). Evidence across brain systems supports a similar adaptive role of functional

reorganization in MS despite widespread pathology by showing that functional reorganization accompanying recovery in this disease limits the impact of damage on behaviour[11-17].

Evidence across functional systems

In this section, we focus on three psychological domains of perception, action and cognition to discuss evidence for functional reorganization leading to functional recovery in MS.

Perception—Visual recovery after acute demyelinating optic neuritis typically occurs within weeks despite permanent axonal loss[18,19]. Plasticity in the visual system contributes to recovery, as the effects of lesions on the optic nerve spread both pathologically[20-22] and functionally[23-30] through the visual pathway. fMRI studies in patients following onset of optic neuritis show reduced activation in the visual cortex in response to visual stimulation of the affected eye[23,24,26-31]. Consistent with adaptive functional reorganization that promotes clinical recovery[28,32], this cortical response increases within 2–6 weeks of disease onset, but remains below that of the unaffected eye[28].

Adaptive functional reorganization occurs at various levels along the visual pathways. During the early period after onset of optic neuritis, activation of the lateral geniculate nucleus (LGN) and visual cortical areas is lower in response to visual stimulation of the affected eye compared with that of the unaffected eye[31]. Later, during recovery, this difference progressively diminishes in both the LGN and the visual cortex[31]. These changes may reflect remyelination of the optic nerve that re-establishes a normal visual input or functional reorganization within LGN that compensates for an impaired optic nerve input to the primary visual cortex. Adaptive changes in early or higher visual areas can also assist in maintaining normal visual function[29-31]. Cortical reorganization within extrastriate visual areas occurs early after onset of optic neuritis and is associated with better visual function[28] and longer-term visual outcome[32]. This early reorganization is associated with recovery independently of other markers of damage in anterior or posterior visual pathways[32]. Orbitofrontal and lateral temporal cortices can be transiently involved in recovery after optic neuritis as part of a dynamic reorganization of visual function in the occipital cortex[28].

Action—Altered functional patterns of sensorimotor activation constitute a disease trait across different forms of MS[33-35]. The extent and type of motor reorganization varies across phases[12,36,37] and stages[38,39] of the disease. After a clinically isolated syndrome (CIS), patients show more widespread recruitment of sensorimotor networks than do healthy volunteers[38]. This functional pattern persists in patients who progress to clinically definite MS[37] and characterizes the acute phases of the disease[12,36]. As the disease advances towards secondary progression, patterns of functional reorganization show an increasingly bilateral distribution and, even for simple motor tasks, involve higher-control sensorimotor areas that in healthy controls are recruited for novel or complex tasks[39].

The magnitude and extent of functional reorganization depends on the extent and severity of lesional[13,40] and extralesional[11,41] brain and spinal cord[42] damage. In patients with normal motor function, greater lesion volume and microstructural damage are associated with more-widespread activation of brain areas[11,13,43]. The increased, bilateral recruitment of

sensorimotor areas may represent an adaptive mechanism that limits the functional impact of MS damage[11]. Alternatively, such changes may be a consequence of reduced ipsilateral deactivation with impaired interhemispheric inhibition owing to callosal damage[40,44]. In either case, the bilateral pattern of sensorimotor recruitment re-lateralises on the contralateral (affected) hemisphere with functional recovery after a relapse. A persistent recruitment of sensorimotor cortex on the ipsilateral (unaffected) hemisphere is associated with poor clinical recovery[36]. Lateralized brain activity with preservation of motor function is a consistent finding across age groups in MS[33]. In addition to the hemispheric re-lateralization, adaptive functional reorganization seems to follow a hierarchy within the motor system, with primary sensorimotor regions being recruited in the benign forms[34] and in the initial stages[39] of MS, whereas secondary motor[45] and multimodal nonmotor[35] areas are involved in the progressive forms of the disease. While damage prompts adaptive functional changes[17,43], disability is associated with a specific altered pattern of hand movement that can reflect maladaptation[17].

Cognition—Deficits in cognitive performance[46-52] and their evolution[53,54] correlate with MS damage. Functional studies investigating cognitive processes such as memory, efficiency of information processing, attention and executive functions[55] have consistently shown that these processes are associated with the activity of wider and more bilateral networks of task-specific regions in patients with MS than in healthy individuals[56-58]. The extent of this recruitment increases progressively with an increased cognitive load[59-61] and becomes more prominent as MS progresses[59], when activity can involve regions outside the specific cognitive domain. Compared with healthy individuals, the magnitude of activation of task-specific networks in patients with MS is reported to be greater in some studies[62], but lower in others[63]. Within cognitive networks, changes in perfusion[64-66] and metabolism[67], as well as in functional and structural connectivity[63,68,69] correlate with cognitive performance. Stronger interhemispheric functional and structural interactions are observed in patients than in controls[63,68,69]. This increased strength of connectivity is associated with damage to specific, task-relevant white matter tracts[69].

Factors influencing adaptive functional reorganization

In MS, individual-specific and disease-related factors influence adaptive functional reorganization and its measurements with imaging methods. *Age* at disease onset may influence the premorbid cognitive functional reserve[61]. After disease onset, a different capacity for brain plasticity[70] and remyelination[71] may help to explain the effect of age on cortical reorganisation and functional connectivity[33,72] that underlie recovery in MS. *Sex* of the patient also affects damage and repair mechanisms in MS[73] through the effects of sex hormones[74,75] and helps to explain clinically relevant sex-specific differences in brain functional connectivity that are observed in MS[76].

The type[12,36,37], location[13,30,42,77], extent[34,39] and severity[11,50,78] of MS *damage* influences adaptive reorganization. Acute inflammation alters functional brain responses[12,28,36,38], with magnitudes that vary depending on the functional system involved[12,28,36,38], as well as on the role of individual brain regions within networks[40,44]. These altered responses return to baseline activity with resolution of inflammation[12,36,37], but a chronic inflammatory state

can produce sustained reorganization of function across brain systems[39] through interference with local mechanisms of brain plasticity[79]. Depending on its location, damage can either interfere with[80] or initiate[13,28,42,77,81] functional reorganization. The extent of brain damage affects substrates for functional functional reorganization[39], potentially with clinically relevant consequences[34,82]. The extent of damage can also affect the regional and network efficiency[83,84]. Clinically, this may be apparent with a higher occurrence of cognitive deficits in the progressive phase of the disease[55,61]. Whereas factors related to brain damage initiate functional reorganization[11], more extensive and irreversible tissue loss is associated with reduced capacity for functional reorganization[12,78,85], which is reflected in a worse clinical outcome[86,87].

Functional reorganization can be maladaptive[6]. Maladaptation with *chronic limb disuse* contributes to disability[17] and may explain the functional differences that are observed among clinical stages[39,88] and among forms[34,80] of MS, beyond the adaptive functional reorganization. Maladaptive plasticity triggered and sustained by disuse may involve multiple functional systems and contribute to disability in multiple functional domains[89]. Although maladaptation may contribute to disability, establishing whether insufficient adaptive reorganization is the basis for disability, and distinguishing between insufficient and maladaptive plasticity is difficult. Future interventional studies that interfere with cortical function or studies assessing concurrent structural changes may disambiguate the relative contributions of maladaptation *versus* insufficient adaptive plasticity.

Promotion of functional reorganization in MS

Adaptive brain *plasticity* offers a flexible substrate for functional reorganization in MS through local re-mapping of cortical representation[13], increased activation in relevant higher-order areas[28,30,77,90] and a shift in interhemispheric lateralization towards the ipsilateral hemisphere[90,91]. A substantial preservation of brain structural architecture allows these mechanisms to act, although at lower efficiency[83], even when MS damage or task demand increase[92-94].

Neuroplasticity offers a substrate for interventions that promote functional recovery in MS, but *stability* of networks is also necessary for adaptive patterns to be retained[70]. Different functional changes are observed in the motor system in childhood-onset *versus* adult-onset MS, which could be explained by age-related differences in the plastic properties of the brain functional systems[72]. In addition, distinct neural systems can have different requirements for plasticity *versus* stability across the lifespan[70]. Functional reorganisation in the extra-striate cortex after ON provides an example of this phenomenon within the visual system[30,70].

Interventions to drive adaptive functional reorganisation

Interventions to drive adaptive plasticity can promote functional restoration by inducing adaptive changes or by predisposing functional systems to plasticity (Figure 1 and Figure 2). Stroke recovery research suggests that functional recovery after brain damage is associated with *normalization* of patterns of functional reorganization[95-97]. Despite the effects of

chronic inflammation on brain plasticity[98], this situation holds true in MS recovery, in both the short-term[14,28,36,37] and the longer-term[14,34].

Training-based interventions—Interference with maladaptation caused by learned disuse[17,99] may be the mechanism through which physical therapy can limit the impact of MS disability[14,100]. Short-term right-hand practice (over minutes) of visuomotor tasks in patients with MS can induce performance improvements that are associated with functional reorganization of ipsilateral (right) sensorimotor regions[14], whose activity is associated with clinical disability[17]. This finding suggests that plasticity changes spreading across functional systems in MS may reflect maladaptation that sustains disability and may be a therapeutic target for recovery-oriented interventions. Longer-term practice (over weeks) of visuomotor tasks also induces performance improvements in patients with MS[14]. The improvements are associated with functional reorganization in cognitive systems that are not involved in visuomotor performance improvements in healthy controls.

Constraint-induced movement therapy is based on overcoming learned disuse. This approach is under evaluation in the treatment of MS[101], supported by its successful application in stroke recovery[102], where it can induce behaviourally meaningful functional changes in the sensorimotor regions of the hemisphere contralateral to the hand moved[9]. The preserved potential for neuroplasticity[14] and motor performance improvements[94] even at higher levels of disease burden suggests that patients with MS patients could benefit from neurorehabilitation irrespective of the initial severity of motor dysfunction[14] (Figure 1), although cognitive systems different from those acting for the same practice in healthy subjects likely contribute to this plasticity in patients[14].

Studies on cognitive rehabilitation in MS that compared the effects of a specific *versus* a nonspecific cognitive treatment have reported conflicting results[103,104]. However, evidence that brain functional patterns subserving an increasing load of cognitive performance before and after cognitive training are comparable in patients with mild or severe cognitive impairment[105] suggests that cognitive training can be beneficial in MS[15] irrespective of the severity of cognitive dysfunction. This finding also suggests that functional plasticity can be enhanced by neuropsychological intervention. Beyond the effect on cognitive dysfunction, such interventions may have the potential to expand the brain's functional reserve[61], especially in childhood MS[106].

Other forms of intervention have been tested in recovery from CNS damage[107-110]. Motor imagery practice (MIP) involves mental repetition of movements, with the aim of improving motor execution[111]. The rationale for MIP is evidence that mentally simulated and physically executed actions, both simple and complex[112], share similar mechanisms of motor control[111]. Through this overlap of neural substrates, MIP may predispose the motor system to the effects of physical therapy[113]. In stroke recovery, MIP provides sufficient repetitive practice to increase use of the affected arm [110] and to change patterns of brain function[114]. Although factors in MS such as cognitive dysfunction and limb disuse could reduce the capacity for mentally simulated actions[115,116], the ability of MIP to drive reorganization of sensorimotor function independently of movement[117] may find clinical application in disabling forms of the disease, in which motor output is severely impaired.

Application of device-based therapies, such as neuroprosthesis for recovery of motor function and computer-based interfaces for cognitive rehabilitation, to rehabilitation of complex behaviours and severe forms of disability is becoming increasingly feasible[15,104,118]. Substantial preservation of brain plasticity in patients across levels of disease burden[14,94] encourages use of these devices for rehabilitation in MS.

Pharmacological and electrical modulation—The rationale for pharmacological and electrical modulation in MS rehabilitation lies in the substrates and mechanisms of brain plasticity[119]. A rich network of intracortical connections can support many organizational structures, allowing for formation of new cortical representations with learning[120,121] or for functional remapping with recovery[13,122]. Persistent changes in the efficacy of intra-cortical connections require a stable form of synaptic modification that is achieved through activity-dependent alteration of the excitatory-inhibitory synaptic balance. These changes constitute *synaptic plasticity*[123], which permits neuronal interconnections to be continuously adjusted as a consequence of their exposure to particular activity patterns. Synaptic plasticity is the basis of network plasticity. Induction of plastic processes depends critically on changes within glutamatergic and γ-aminobutyric acid (GABA)-ergic interneurons[124,125]. Although neuromodulators induce little or no change in basal neuronal activity, they can potentiate or attenuate responses evoked by such neurotransmitters[126].

Pharmacological interventions in recovery strategies can increase or prolong the efficacy of rehabilitation by increasing the susceptibility of relevant nodes or systems to the effects of physical or cognitive interventions[107]. Modulation of glutamatergic activity with potassium-channel blockers enhances the excitability of the motor cortex and conduction along corticospinal pathways in patients with MS[127,128], providing a rationale for testing the effects of modulation of glutamatergic tone in motor recovery[129]. Cholinergic agonism modulates synaptic plasticity in the hippocampus[130,131]. Modulation of cholinergic tone through acetylcholinesterase inhibition enhances cognitive function in MS patients with memory deficits[132]. Functional changes in the prefrontal cortex, as well as changes in its functional connectivity, may underlie the efficacy of this intervention[16,133] (Figure 2). Dopamine modulates cortical excitability via changes in synaptic plasticity[134] that are relevant for motivational and motor aspects of learning[135]. As in stroke recovery[136], modulation of dopaminergic frontal projections in MS might potentiate aspects of motor recovery and memory consolidation[135]. Serotonin also regulates synaptic plasticity and cortical excitability[137-140]. Use of serotonin-reuptake inhibitors in association with physical therapy has produced beneficial effects on motor outcomes in patients who are moderately impaired after stroke[141]. Modulation of multiple neurotransmitter systems to promote stroke recovery has been attempted with amphetamines,[107] which act primarily through noradrenaline and dopamine signalling and enhance arousal and attention that is relevant for learning and recovery[142]. L-amphetamine sulphate has been tested for treatment of cognitive dysfunction in MS. They significantly improved performance in learning and memory tasks[143,144], as well as speed of processing and working memory[145].

Repetitive transcranial magnetic stimulation (rTMS) interferes with or potentiates the function of specific cortical regions[146]. In stroke recovery, rTMS can improve motor function by re-establishing the functional interhemispheric balance through reduction of

interhemispheric inhibition or by increasing the excitability of damaged circuits[147]. In MS, rTMS may limit the effect of functional interhemispheric imbalance between motor regions and may induce remote effects on the excitability of spinal circuits in patients suffering from spasticity[148,149]. Transcranial direct current stimulation (tDCS) modulates synaptic plasticity by altering cortical excitability[150]. Decreased GABAergic tone, which releases latent cortico-cortical projections from tonic inhibition, is a mechanism of rapid cortical plasticity that can facilitate recovery[120]. tDCS can predispose brain plasticity mechanisms to learning[151] and recovery[152] through modulation of this GABAergic tone. The therapeutic potential of electrical stimulation is under investigation for stroke recovery, but its possible application to MS recovery remains to be explored.

The presence of cortical pathology in MS challenges attempts to develop pharmacological and electrical interventions that modulate the function of specific brain systems as pathological changes may alter cortical excitability and thus interfere with the desired effects of interventions.

Beyond pharmacological and electrical interventions, the question remains open as to what effect pharmacological modulation of inflammation with disease modifying treatment has on mechanisms of brain plasticity[79].

Imaging adaptive functional reorganization in MS

Promotion of functional restoration requires optimization of methods to detect the effects of interventions and to improve the efficiency of studies. fMRI has been widely used in studies on recovery in MS[153]. It characterizes functional reorganization at the systems level[154], as generation of an fMRI signal correlates with neural activity. However, the fMRI signal is only indirectly neural in origin, and disease-related factors and therapeutic interventions can further complicate interpretation of the signal[3] (Figure 3). Therefore, the use and interpretation of fMRI as a measure of neural activity in studies on neuroplasticity and recovery requires methodological consideration[3].

Interpretation of fMRI signal in disease and in interventional studies

The blood oxygenation level-dependent (BOLD) signal is the image contrast most commonly used in fMRI studies (Box 2). Comparison with electrophysiological measurements suggests that the BOLD signal most closely corresponds to pre- and postsynaptic processing of incoming afferent signals and intracortical processing, such as are represented in local field potentials[155-157] rather than the spiking output of a particular region. Proportional increases or decreases in local excitation and inhibition are likely to lead to increases or decreases, respectively, in the local energy demand and, therefore, in the BOLD signal[155-157]. Net excitation is also likely to lead to BOLD signal increases, whereas the fMRI response to a net inhibition is probably more circuit-dependent owing to lower energy demands of reduced excitation but increased energy requirement for the inhibitory processes[155-157].

The origin of the BOLD signal is vascular, so neurovascular coupling must remain intact for fMRI to provide a faithful representation of alterations in neural activity. Not only should

the chemical signalling between neurons, astrocytes and cerebral arterioles be preserved, but so should the biophysical coupling between the vascular response and the BOLD signal. This coupling is embodied in the concept of vascular reactivity, defined as the capacity of the vasculature to augment blood flow and generate a BOLD response following a vascular stimulus.

Alteration of the physiological properties of the BOLD signal can occur with age, in chronic inflammatory states or with therapeutic interventions[158-160] (Figure 3). *Age* can affect the fMRI response independently of other pathological factors. A reduction of task-induced BOLD contrast associated with reduced baseline cerebral blood flow (CBF) and baseline cerebral metabolic rate of oxygen ($CMRO_2$) has been demonstrated in the ageing brain[161]. Baseline CBF has been shown to modulate task-related BOLD signal[162]. Vascular reactivity assessment using carbon dioxide (CO_2) has suggested a reduced ability of blood vessels to respond in the ageing and diseased brain[163,164]. In addition to alterations in vascular behaviour, neurodegenerative diseases and even a genetic predisposition for such diseases are likely to modify CBF, cerebral blood volume (CBV) and $CMRO_2$ and, therefore, the BOLD response[165,166].

Disease or *interventions* can induce changes in baseline neural activity and vascular response, which are likely to modulate the BOLD signal in response to a task[167], leading to either over- or underestimation of their true modulatory effects on brain activity (Figure 3). Altered fMRI responses have been demonstrated in circumstances of altered underlying cerebral physiology[168]. In MS, vascular and metabolic changes have been described[169,170]. Abnormal perfusion occurs in enhancing[171] and nonenhancing[172] MS lesions, as well as in normal-appearing brain tissue in patients with MS[169]. Both white and grey matter can be affected by perfusional changes that result from damage. This perfusional changes can differ across disease phases and forms[173]. Baseline $CMRO_2$ and venous CBV can also be reduced in MS[174]. Furthermore, a more systemic vascular dysregulation can arise from production of inflammatory molecules and from astrocyte dysfunction[169], which can alter neurovascular coupling through a vasoconstrictive effect[169] or through impaired buffering of ions and neurotransmitters[175]. In addition to disease-associated alterations, therapeutic interventions can induce changes in fMRI responses through their effects on brain plasticity. Their effects on BOLD response may also differ from those in healthy individuals, as therapeutic interventions can interact with damage.

Given the complexity of the processes leading to generation of BOLD signal and the additional confounders generated by factors such as age, pathology or interventions, methods to improve the interpretability of the fMRI signal are needed to characterise mechanisms and aid in the development of interventions for functional recovery in MS.

Improving interpretability of fMRI signal

Controlling for factors that modulate the BOLD response to neural activity improves the interpretability of fMRI[3] (Table 1). However, use of a control task to explore the functional system specificity of an intervention is useful for ruling out global modulation of signalling or vascular reactivity induced by the disease or the intervention. Also, resting fMRI provides an alternative approach to studying functional plasticity that avoids the confounding effect

of task-related performance. This approach has been used to explore spontaneous and intervention-driven functional reorganization in MS[15,80,81,176-178]. It provides a powerful tool in recovery studies as changes in local *versus* distant connectivity can be characterized despite inter-individual differences in spontaneous or intervention-driven behavioural changes. Resting fMRI can also help to disentangle the contribution of insufficient adaptive *versus* undesirable maladaptive plasticity to clinical status and to changes in clinical status with intervention. However, given the absence of associated behavioural information in resting fMRI, use of this approach in disease and interventional studies requires similar methodological consideration to task-based fMRI.

Measurement of baseline perfusion and of perfusion responses to a task can help to control for differences in baseline BOLD signal[161,162,165,179], which is relevant when assessing the effect of interventions in patient groups that are affected by different levels of inflammation or are undergoing different types of pharmacological interventions. Vascular reactivity, tested using a vascular stimulus such as CO_2[180], can be factored into a subsequent analysis of task-related BOLD signal changes[181] to separate the effect of disease or intervention on the vascular *versus* the neuronal component of the BOLD signal[159]. Combination of fMRI approaches with simultaneous or delayed electrophysiological recording - that is, electroencephalography, magnetoencephalography or TMS - can further contribute to elucidation of the origin of BOLD signal changes[3]. This combination approach is particularly useful for clarifying the neural correlates of an increased or decreased BOLD signal[128] and, thereby, the mechanisms underlying therapeutic interventions. Calibrated fMRI, in which task-related fractional changes in $CMRO_2$ are derived from calibration of BOLD signal relative to changes in CBF[182,183], has been used in pharmacological studies in the healthy brain[159,184] with the expectation that $CMRO_2$ changes reflect the underlying neural activity better than BOLD signal alone. In addition to controlling for potential confounding factors, the measurement of cerebral physiology might provide novel markers of recovery or treatment effects. Arterial-spin labelling measures of CBF, for example, are more stable markers of resting levels of brain activity over long time periods than are BOLD signal measures[185], which is relevant to disease evolution and treatment[158]. Furthermore, regional measures of vascular reactivity[163] and CBF may help to determine inflammatory status[172] and thus assess the effects of anti-inflammatory treatments and their effects on brain plasticity in MS.

Efficient study designs would facilitate the development of interventions to promote recovery. Multicentre fMRI studies are feasible and reliably informative in MS[91]. In multicentre settings, longitudinal studies, which are required when testing interventions to promote recovery[186], can provide reproducible fMRI measures[187].

Several studies in motor recovery in MS have analysed functional and effective connectivity using sophisticated statistical approaches to establish the strength of activation and synchrony between specific brain areas[77,178]. Graph theory approaches that model effectiveness of information transfer within brain networks can enable assessment of the effect of individual factors, disease and intervention in dynamically changing brain systems[76,83,188].

Functional changes in specific regions can be particularly informative in assessment of restorative therapies. 'Recovery-weighted' maps, in which patient-specific[28,30,63] and performance-related[91] functional responses are associated with a favourable clinical status[63] or outcome[33,34], can be useful for testing the effects of interventions[9]. Similarly, the development of high-resolution methods to study difficult-to-access anatomical regions relevant for recovery such as the LGN can help in understanding aspects of recovery that can be manipulated early after acute damage[31].

In studies on recovery, fMRI is often combined with structural information in an attempt to capture brain plasticity. Models that combine visual responses as measured on fMRI with optic nerve structure and measures of visual function can determine the contribution of functional reorganization to clinical function after accounting for structural factors[28]. Combination of functional connectivity measures with measures of structural damage to specific white matter tracts is also used to investigate the relationship between structural and functional abnormalities in patients with MS[90]. Structural imaging can be used in combination with functional imaging in recovery studies to investigate the bases for individual variation in neuroplasticity[189] and recovery[190], to demonstrate structural plasticity accompanying functional plasticity and to characterize the time course of these concurrent changes[191]. A detailed discussion of structural imaging methods to investigate structural repair is beyond the scope of this Review. Given the close interplay between systems-level functional and structural plasticity, opportunities and limitations of structural imaging methods, which may be relevant to investigate structural repair in MS[153] and may be similarly affected by disease or interventions, are briefly discussed in Supplementary Box 1 online.

Conclusions and future directions

Despite substantial progress in the field of functional recovery, MS continues to be the major cause of chronic neurological disability in young adults, and development of therapeutic strategies to promote functional recovery remains challenging. Review of the Literature highlights difficulties of confidently interpreting results from single studies or of combining results from different studies because of uncertainties about the homogeneity of patient groups, standardization of interventions, whose biological effects can be characterized and quantified using both clinical scales and objective (imaging or electrophysiological) measures, a lack of sensitive surrogate markers of recovery or an understanding of expected treatment effect sizes that could contribute to prospective powering of studies. A path forward will involve development of new kind of study designs, optimized for assessing specific mechanisms of recovery and incorporating clinically relevant outcomes, with testing of specific hypotheses related to the underlying neurobiological mechanisms with which interventions promote recovery. A combined strategy involving a strong biological rationale and monitoring of functional and structural reorganization using brain imaging methods should form the basis for scientifically informed neurorehabilitation in MS. Using this approach, effects of interventions can be quantified and compared with clinically-relevant, sensitive and reproducible measures in selected clinical cohorts (Box 3). As in stroke research, restorative strategies in MS are building on emerging understanding of neural plasticity. Their progress, therefore, is

inherently cross-disciplinary and relies on more complex, multimodal approaches, beyond the purely behaviour-centred studies.

Experience gained from other neurological conditions provides a powerful framework in which models of recovery and neurorehabilitation can be constructed and tested[154]. Development of new strategies to promote recovery, and of imaging markers to measure effects of therapeutic intervention, however, needs to take place within the specific pathological context of MS. The chronic and diffuse nature of MS pathology poses challenges, as effects of interventions need to be sustained and to operate across multiple brain systems. In addition to adaptive plasticity, maladaptive reorganization accompanying chronic disuse can occur, presenting a further challenge to recovery. Limited, direct evidence from studies in MS encourages manipulation of adaptive plasticity with therapeutic interventions, but our knowledge of brain plasticity in MS derives mainly from observational studies without external inducement of plasticity. Further testing in controlled interventional studies is essential if we are to develop an understanding of how to effectively promote adaptive plasticity in MS and how to translate such methods into clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1

Criteria for the definition of behaviourally relevant brain functional reorganization after brain damage. Recovery studies in the fields of stroke and MS suggest that behaviourally meaningful functional reorganization - that is, adaptive functional reorganization - can be defined if:

1. There is a relationship between extent of changes of functional patterns and associated pathology
2. Altered patterns of functional activation accompanied by preserved or completely recovered behaviour
3. Learning or rehabilitation induce similar changes in functional activation
4. Facilitation of reorganization increases the rate of, or the potential for recovery
5. Interruption of reorganization processes and/or maladaptation results in functional impairment

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Box 2

The neurophysiological basis of functional MRI. Functional MRI (fMRI) has millimetre-scale spatial resolution, providing a large-scale average of neural activity. The parameter measured by this imaging technique is the blood oxygenation level-dependent (BOLD) signal, which is principally affected by changes in the local balance between neuronal excitation and inhibition. Increased neural activity results in increased cerebral metabolic rate of oxygen ($CMRO_2$) and local vasodilatation. As a consequence, cerebral blood flow increases. The fractional increase in blood flow is greater than the fractional increase in $CMRO_2$. This difference reduces the quantity of (paramagnetic) deoxy-haemoglobin in the veins and is equivalent to increased oxygenation, which increases local magnetic field homogeneity around capillaries and veins and, thereby, increases net signal intensity in that area. This change in BOLD signal varies depending on the magnetic field strength, the brain region and the underlying physiology or pathology. Within a scan, periods of active stimulation ('ON' condition) are contrasted with rest periods ('OFF' condition). The choice of baseline is crucial in the interpretation of fMRI data.

The most powerful experimental designs use equal-duration alternating ON and OFF periods (*block design*), each lasting 10-60 s. Brief stimuli can be used in *event-related designs* where the functions under investigation dictate. Investigations of resting-state activity, in which the volunteer does not perform a particular task, have grown in popularity in recent years, especially in patient populations, removing the potential complication of disease-associated impaired task performance. These investigations seek to identify temporally co-varying BOLD signals, which are thought to reflect dynamically co-varying levels of neural activity, from different brain regions. Such signals are thought to represent functional connectivity between the brain regions in question. This approach can identify networks of brain regions that could underlie a specific function, such as motor output or vision[192], and can be used to detect their potential modulation in disease.

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Box 3

Considerations for future studies to promote functional recovery in MS.

Type of study

Hypothesis-driven studies are preferable when targets of intervention are known. Translational studies, from bench to bedside, should be encouraged. Exploratory methodologies can be used for identification of potential new therapies or targets.

Design

Optimized trial designs (for example, sequential, adaptive or enrichment methodologies) should be prioritized over traditional trial designs. Appropriate control groups are essential. A post-intervention study phase is desirable to confirm the effect of interventions and to test for sustained effects.

Groups

Cohorts with disabilities should be prioritized when investigating the potential benefits of new interventions. Nondisabled cohorts can be studied to define biological mechanisms of successful recovery. They may be also considered for studies of interventions that have potential to increase the capacity for recovery by delaying accrual of disability Eligibility criteria for study group should be based on “rehabilitation criteria” (performance over disease characteristics), when effects of interventions are tested, or on “standard clinical criteria” (disease characteristics over performance), when the influence of specific disease characteristics on effects of interventions is to be tested.

Sample size

Fixed sample size or adaptive sample size re-estimation can be considered, depending on the type of study design.

End point

The study end point should be clinically relevant. Both clinical and paraclinical measures such as imaging should be collected to define mechanisms of therapeutic benefit. Efforts should be accelerated to better validate imaging or other paraclinical measures of brain recovery. Patient-related outcome measures provide an important complementary perspective.

Interventions

Behavioural, pharmacological or electrophysiological interventions should all be considered. Interventions and key aspects of imaging or other paraclinical measures should be standardized as much as possible to allow comparisons between studies. To facilitate the development of such standardised methods, the scientific community should work towards sharing of methodology and data.

Analysis methods

Hypothesis testing and exploratory studies should be clearly identified as such and appropriate statistical approaches used for each. Confidence intervals should be regularly

reported and consideration should be given to the potential effects of heterogeneity in patient populations. When imaging is combined with behavioural studies, multimodal approaches are desirable.

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Search strategy and selection criteria

References for this Review were identified through searches of PubMed using the search terms “functional reorganization”, “brain plasticity”, “recovery”, “rehabilitation”, “pharmacological modulation” and “MRI” from January 1949 until April 2012. Articles were also identified through searches of the authors’ own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to this Review.

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Key points

- Evidence across brain systems supports a behaviourally relevant role for neuroplasticity in multiple sclerosis (MS) across ages, stages and phases of the disease, which is preserved despite widespread pathology.
- Together with adaptive plasticity, maladaptive plasticity can occur owing to disuse with impairment and may contribute to disability.
- Interventions that drive neuroplasticity can promote functional restoration by inducing adaptive changes or by predisposing functional systems to adaptive plasticity.
- Individual and disease-related factors influence both spontaneous and intervention-driven adaptive functional reorganization, as well as its assessment using imaging.
- Improving the interpretability of functional MRI measures is important for characterization and quantification of the effects of recovery interventions and, thereby for development of recovery-oriented strategies.

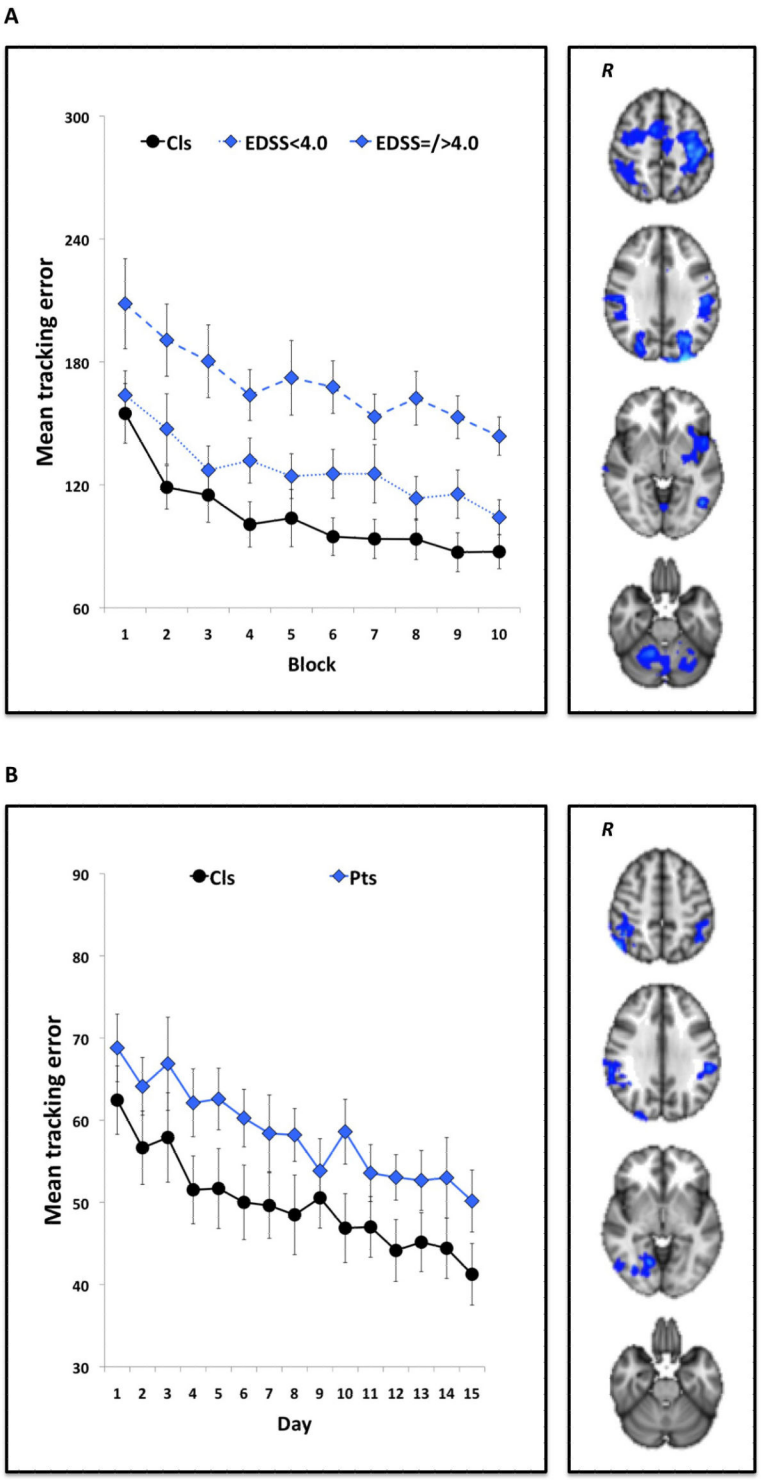

Figure 1.

Non-pharmacological modulation of brain plasticity in MS[14,94]. Patients with MS and healthy volunteers performed a visuomotor task in which they tracked a continuously moving bar on a computer screen by altering pressure applied to a handle held in the right

hand. The task was performed in blocks of 38 sec. Participants practised the task in short-term (10 blocks for a total of ~25 min) and in the longer-term (daily for 15 days consecutively) settings. Performance was measured as the mean tracking error across each block (short-term) or day (longer-term) of practice. During the first and last session, participants underwent fMRI scanning. As depicted in the graphs, short-term (a) and longer-term (b) task practice significantly improved visuomotor performance in both healthy controls and patients with MS, across levels of disability according to EDSS scores. As shown in the fMRI scans, these performance improvements were associated with a reduction in blood oxygenation level-dependent signal in brain regions involved in visuomotor integration. Abbreviations: EDSS, Expanded Disability Status Scale; fMRI, functional MRI; MS, multiple sclerosis; R, right hemisphere. Permission obtained from SAGE Publications © Tomassini, V. *et al. Mult. Scler.* **17**, 103–115 (2011), and Tomassini, V. *et al. Neurorehabil. Neural Repair* **26**, 581–593 (2012).

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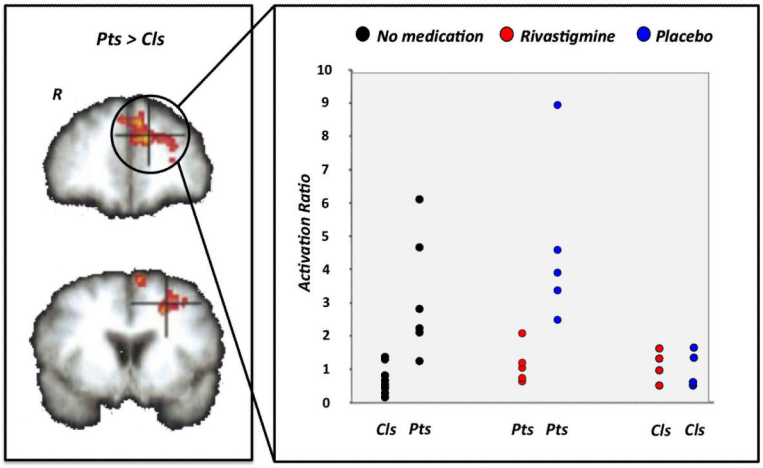

Figure 2.

Pharmacological modulation of brain plasticity in MS[16]. Patients with MS and healthy volunteers underwent a counting Stroop task during fMRI scanning. Patients had comparable cognitive performance to controls, but a significantly greater BOLD signal change in the left prefrontal cortex - a difference that reflects functional reorganization. BOLD signal changes in these regions correlated with cognitive performance and brain volume. A functional score, the activation ratio (AR), representing the ratio between the magnitude of prefrontal cortex activation on the left (found in MS patients) relative to right hemisphere, was calculated to test the effect of pharmacological modulation of brain adaptive plasticity with rivastigmine, a cholinesterase inhibitor. Before rivastigmine administration or following administration of placebo, mean AR in patients was greater than in controls. After rivastigmine administration, mean AR in patients was reduced to within the range of controls. Abbreviations: BOLD, blood oxygenation level-dependent; fMRI, functional MRI; MS, multiple sclerosis; R, right hemisphere. Permission obtained from Oxford University Press © Parry, A. M. *et al. Brain* **126**,2750–2760 (2003).

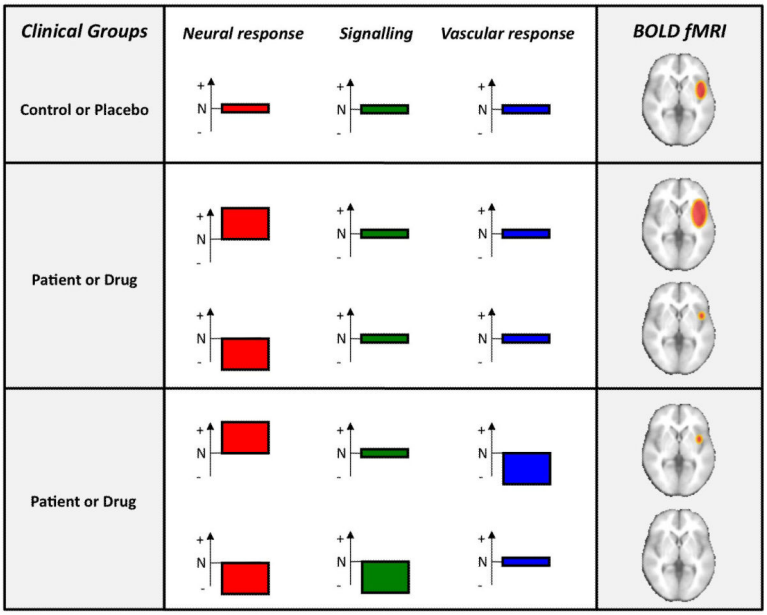

Figure 3.

Effects of disease and pharmacological interventions on generation of BOLD fMRI signal[3]. The graphs illustrate normal (N), elevated (+) or reduced (−) levels in processes that generate the measured BOLD signal. These processes include neural and vascular factors such as signalling to the vasculature and vascular responsiveness. **(a**) A schematic fMRI activation map in a control group or under placebo administration. **(b)** Changes in neural activity induced by disease or drugs are correctly reflected in the final statistical map when the confounding effects of signalling and vascular responses are taken into account. **(c)** Changes in neural activity induced by disease or drugs are incorrectly reflected in the final statistical map because of the intervening confounds of altered neurovascular signalling or vascular responsiveness. Abbreviations: BOLD, blood oxygenation level-dependent; fMRI, functional MRI. Permission obtained from Elsevier Ltd © Iannetti, G. D. & Wise, R. G. *Magn. Reson. Imaging* **25**, 978–988 (2007).

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Table 1

Potential confounding factors affecting BOLD signal generation in MS studies and strategies to overcome them.

Source of fMRI signal	Confounding factors	Strategy to control for confounding factors
Neural signalling	Disease-related or intervention-related increases or decreases in brain activity	Simultaneous or delayed electrophysiological recording
Neurovascular coupling	Disease-related or intervention-related effect on vascular response to changes of neural activity	Measure vascular reactivity (for example, with carbon dioxide challenge)
Vascular compartment	Disease-related or intervention-related differences in baseline perfusion levels	Measure baseline perfusion Measure perfusion response to a task