PLASTICITY IN MULTIPLE SCLEROSIS: FROM MOLECULAR TO SYSTEM LEVEL, FROM ADAPTATION TO MALADAPTATION

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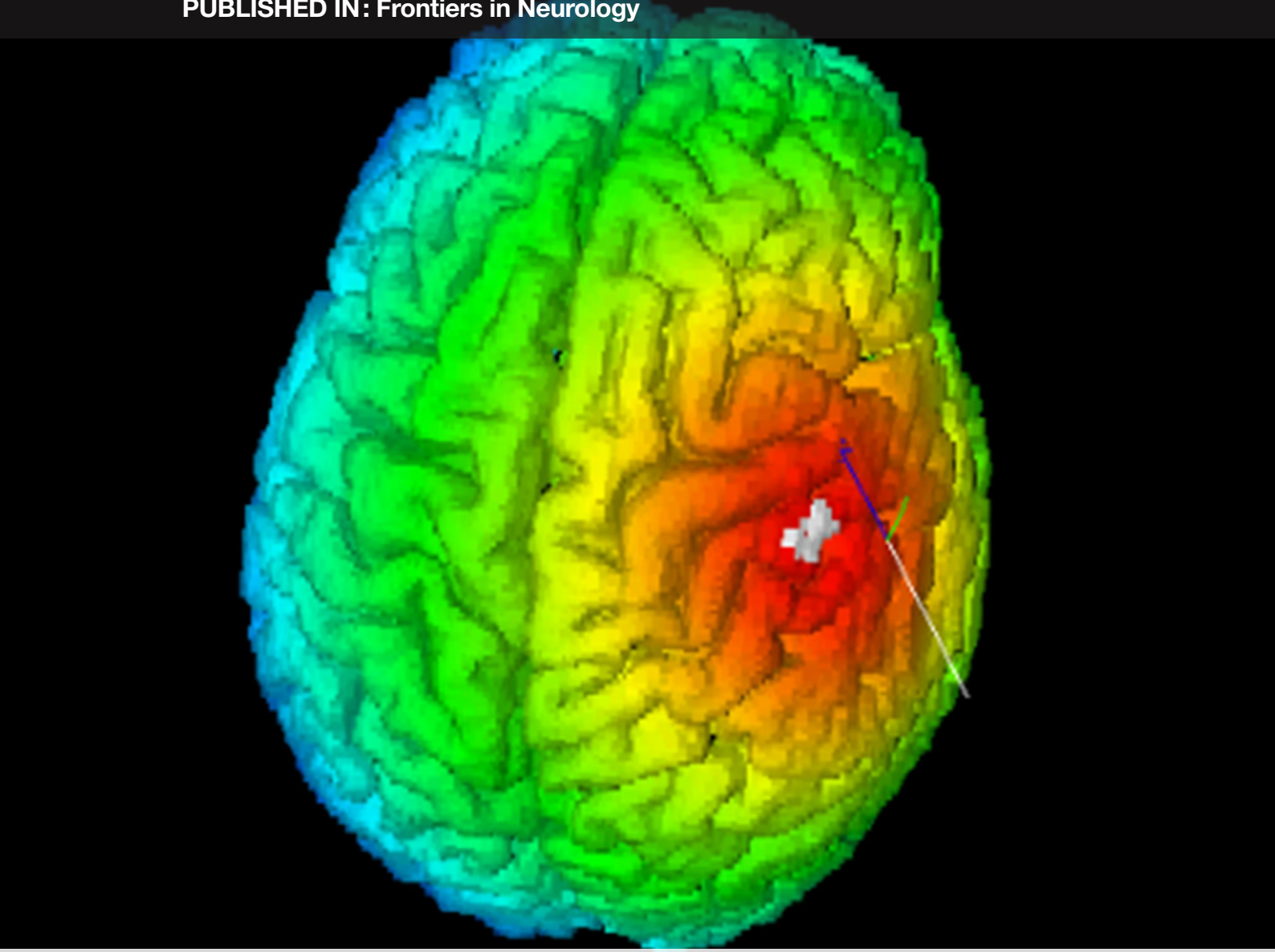

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PLASTICITY IN MULTIPLE SCLEROSIS: FROM MOLECULAR TO SYSTEM LEVEL, FROM ADAPTATION TO MALADAPTATION

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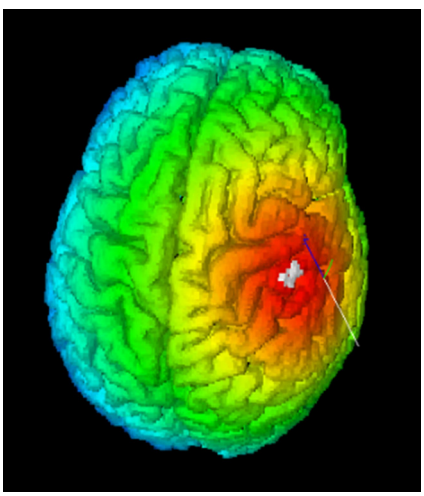

Neuromodulation treatment to reduce MS fatigue. Personalized transcranial direct current stimulation electrode positioned over the whole body S1 area of one single subject.

Image by: Tecchio F, Cancelli A, Cottone C, Ferrucci R, Vergari M, Zito G, Pasqualetti P, Filippi MM, Ghazaryan A, Lupoi D, Smits FM, Giordani A, Migliore S, Porcaro C, Salustri C, Rossini PM and Priori A (2015) Brain plasticity effects of neuromodulation against multiple sclerosis fatigue. Front. Neurol. 6:141. doi: 10.3389/fneur.2015.00141

This research topic aims at providing a state of the art update on neuroplasticity in humans with multiple sclerosis. It summarizes advances in plasticity research as achieved by a variety of techniques, in the motor as well as visual and cognitive domain. We are confident that this collection of articles broadens the view across systems and techniques and widens our understanding of this exciting field of research.

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EDITORIAL
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Editorial: Plasticity in Multiple Sclerosis: From Molecular to System Level, from Adaptation to Maladaptation

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The Editorial on the Research Topic

Plasticity in Multiple Sclerosis: From Molecular to System Level, from Adaptation to Maladaptation

Multiple sclerosis (MS) is an inflammatory disease that affects the central nervous system (CNS) by demyelination and direct axonal injury (1). Decades of research have focused on pathophysiological issues of the disease and, at least for the relapsing-remitting type of MS, have achieved considerable progress with respect to the prevention of relapses and accumulation of MS-related clinical impairment (2). However, only recently there is increasing awareness that the individual course of MS might not only be governed by neuroimmunological properties of the disease but also determined by the innate capacity of the CNS to overcome functional constraints related to MS pathology, i.e., by the patient's individual resilience. Accordingly, variation in brain plasticity is believed to play a crucial role in explaining interindividual differences with respect to the clinical course as well as to discrepancies between functional impairment and magnetic resonance imaging (MRI) findings in patients with MS (3, 4).

Plasticity occurs at multiple levels in MS, from cells to synapses, from myelin to axons, from individual regions to large-scale brain networks [reviewed in Ref. (5)]. A growing body of evidence supports the notion that the course of MS and its extremely heterogeneous clinical manifestations might be the net result of disease burden and compensatory/reparative capacity. As a consequence, identifying what can be considered as "positive" plasticity and what, on the contrary, is a maladaptive reorganization is a very attractive goal that might help to develop therapeutic strategies able to promote the individual adaptive capacity.

This research topic provides an update on plasticity in MS. Mirroring different points of view on this topic, the collection includes a variety of different research tools, including behavioral, neurophysiological, and neuroimaging techniques, which have addressed neuroplasticity at different systems, from motor to visual and to cognitive.

Broadening our view into the cellular level, Carandini et al. review the potential role of microvesicles, i.e., spherical membrane vesicles, which are held to play a role in cell communication, in the pathogenesis of MS. Released by microglia and infiltrating macrophages, microvesicles may not only spread inflammatory signals but may also alter neuronal functions, and therefore influence synaptic plasticity.

Houdayer et al. provide a summary of the neurophysiological tools that are widely used to study cortical dysfunction in MS, with emphasis on event-related EEG oscillations, long-latency reflexes,

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and transcranial magnetic stimulation (TMS). In the second part, the authors present neurophysiological paradigms modulating cortical plasticity in MS, such as repetitive TMS or transcranial direct current stimulation (tDCS), which – above their great value in research – have brought some promising results as add-on treatments.

Along this line, Tecchio et al. report the effects of five sessions of tDCS targeting the bilateral whole body somatosensory area (S1wb) and the hand sensorimotor area, respectively, in 21 relapsing-remitting MS patients with fatigue. They describe a 27% reduction on the modified Fatigue Impact Scale following S1wb treatment, thereby pointing out the future therapeutic potential of non-invasive brain stimulation techniques.

Pantano et al. report findings derived from the analysis of motor network plasticity, using either active functional MRI (fMRI) tasks or resting-state investigations. The possibility of manipulating motor network plasticity by means of drugs or motor practice in order to obtain a better clinical outcome is also discussed.

How an improved understanding of the neural processes underlying functional recovery might contribute to guide rehabilitation strategies and the development of novel recovery interventions is introduced by Lipp and Tomassini.

Gallo et al. discuss the role of adaptive functional changes at the level of the visual cortex, which have mostly been assessed by photic-stimulated or resting-state fMRI following acute optic neuritis (ON). Data support an adaptive role of neuroplastic changes at the level of the occipital extrastriate cortex, which might promote visual recovery after ON. The authors speculate that models of visual plasticity might prove useful to evaluate the effect of plasticity promoting molecules.

By analyzing current discrepancies in the literature on cognitive network function (and dysfunction), Schoonheim et al. propose a model of functional reorganization, which moves from the analysis of single regions and/or networks to a more holistic network model of the entire brain, which can be explored, for instance, by using graph analysis. The need to validate this model in a longitudinal framework is also emphasized.

The notion that the use of novel approaches would provide a better understanding of the role of functional plasticity in improvement following cognitive training is also supported by the case-based fMRI series presented by Hubacher et al., who describe the occurrence of different and opposed response patterns after the same training in different subjects.

Starting from the clinico-pathologic dissociation between MS disease burden and cognitive functions, Sumowski accounts for the cognitive reserve hypothesis, which postulates that enriching life experiences protect against cognitive decline in the face of age and neurological disease. Test algorithms to identify MS patients at greatest risk for future cognitive decline may allow probing early interventions, like intellectual enrichment programs. Aside from such clinical measures, MRI-based markers will provide measurable proxies for estimating the individual reserve.

The importance of identifying adaptive versus maladaptive neuroplasticity associated with specific cognitive rehabilitation programs in MS patients with the main disease clinical phenotypes to foster the validation of the most effective cognitive rehabilitation interventions for these subjects is defended by Chiaravalloti et al.

Enzinger and Fazekas provide a critical revision of the development and current state of imaging techniques to assess MS-related morphologic damage and their contribution to understand the clinical consequences of MS (disability, and also cognitive problems and fatigue). They discuss why measurement of brain damage by structural MRI alone is not enough to comprehensively appreciate the consequences of the disease, although it is ideal for specific questions (e.g., assessment of disease activity, remyelination, or evolution of atrophy). All of this prompts toward an integrated use of structural and functional imaging techniques to assess disease progression in these patients.

Finally, Flachenecker summarizes current scientific evidence of MS rehabilitation. Given the main goal of rehabilitation therapy, i.e., facilitating adaptation and reorganization within the CNS, rehabilitation may rightly be regarded as "applied neuroplasticity." The author points to the need of further carefully designed studies on the effectiveness of neurorehabilitation including both clinical outcomes and neuroplastic measures in order to bridge the gap between basic science and clinical experience.

This Research Topic thus offers a synopsis of recent advances of plasticity research in MS. It aims at broadening the view across systems and techniques and at stimulating further studies on this emerging and fascinating topic.

AUTHOR CONTRIBUTIONS

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REVIEW
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Microvesicles: what is the role in multiple sclerosis?

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Microvesicles are a recently described way of cell communication that has been implicated in a number of biological processes, including neuroinflammation. Widely investigated as biomarkers in oncology and neurological disorders, little is known of the role of microvesicles in the pathogenesis of diseases such as multiple sclerosis (MS). Several evidences suggest that pro-inflammatory microglia and infiltrating macrophages release microvesicles that spread inflammatory signals and alter neuronal functions. We review here available information on microvesicles, with a special focus on microglia and macrophage microvesicles, in the pathogenesis of MS, and as potential biomarkers and therapeutic targets.

Keywords: microvesicles, multiple sclerosis, exosomes, ectosomes, horizontal communication, biomarkers, microglia

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Introduction

Since its first steps neurobiology focused the most part of its efforts on trying to elucidate in great detail the physiology of neurons with very few attention about the other cell types (as a whole referred as glia) because considered as important as just a glue for the neuronal networks assembly and stabilization (1).

Growing attention has been gradually given to glial cells since the demonstration of the multiple roles they have, not only in the maintenance of the brain environment but also in crucial steps of the synaptic transmission: oligodendrocytes and Schwann cells sustain the saltatory conductance of the electric stimuli by insulating specific regions of the axonal tracts, astrocytes provide neurons with some already metabolized neurotransmitters and together with microglia participate in information processing at the level of single synapses or neuronal networks (2). The contribution of microglia to neuronal activity was initially suggested by the observation that multiple contacts occur between microglial cells and neurons at the synaptic terminals (3). In fact, in the developing and adult nervous system, microglia, owing to its phagocytic activity, can physically remodel synapses in a neuronal activity-dependent manner by eliminating excessive or unused contacts (synapse pruning) (4), leading to the formation and consolidation of rearranged synapses driven by sensory experience (synapse maturation) (3, 5–8). In hippocampal neuron cultures, microglia can sustain long-term potentiation (LTP) (9, 10), an observation supported *in vivo* by significant learning and memory deficits in microglia-depleted mice (11). In pathological brain conditions also the basal glutamatergic and GABAergic transmission can be regulated by microglia cells as a consequence of the stimulatory effects of damaged cells-derived ATP on their secretion (12–15); in fact, brain-derived neurotrophic factor (BDNF) secreted from ATP-stimulated cells can tune both excitatory and inhibitory neuronal circuits activity and also support neuronal survival during inflammation (16). In addition, extracellular ATP strongly induces the generation of microvesicles

by plasma membrane shedding from responsive cells (17). In this complex picture, microvesicles released by microglia have been shown to cause an excitatory-inhibitory unbalance. They stimulate spontaneous and evoked glutamate transmission in excitatory neurons by facilitating presynaptic release probability (18), while decrease spontaneous GABAergic tone (19). Potentiation of excitatory transmission seems to reside in the capability of microvesicles to interact with neurons and modulate the levels of sphyngosine, which has been found to have a strong impact on neuronal firing activity (20–22), by acting on the lipid metabolizing enzyme acid sphingomyelinase (aSMase). Reduction of GABAergic transmission is instead mediated by endocannabinoids, which are highly enriched in microvesicles, through the activation of presynaptic CB_1 receptors (19). Here, we will review current knowledge on myeloid cells and their release of microvesicles in neuroinflammatory disorders such as multiple sclerosis (MS).

Myeloid Cells in MS

Myeloid cells, encompassing microglia, monocytes-derived macrophages and resident-CNS macrophages, play an important role in the pathogenesis of MS and its animal model experimental autoimmune encephalomyelitis (EAE). MS and EAE, in fact, are characterized by the rapid recruitment of blood-borne monocytes, the reaction of resident microglia and perivascular macrophages, along with the recruitment of T cells (23). Many studies have demonstrated that reactive microglia and macrophages can be found in white matter lesions (early and late) and in gray matter subpial lesions (24). Macrophages within CNS lesion sites are difficult to distinguish from reactive microglia, since they both are amoeboid-shaped and express the same antigenic markers. Many authors refer to these cells collectively as macrophages/microglia or as mononuclear phagocytes. The importance of these cells in the MS pathogenesis is demonstrated by several EAE studies: a marked reduction in disease severity is observed when reactive microglia/monocytes are killed either by ganciclovir administration to EAE induced in CD11b-HSV-TK mice (25), or using clodronate liposomes (26). Moreover, inflammatory monocytes ($CCR2^+$ and/or Ly-6C high) have been shown to promote EAE progression, while CCR2-deficient mice are resistant to EAE (24, 27, 28). The monitoring of microglial reaction *in vivo* was made possible by the discovery of the radiolabeled molecule 11C(R)-PK11195177, a ligand for the benzodiazepine receptor whose expression in the CNS is increased in reactive microglia (29). A recent study showed correlation between clinical disability and PK11195 PET binding in the cortex of MS patients (30). Both MS and EAE are characterized by a dramatic increase in bound radiolabel in both inflamed and normal appearing white matter on MRI. The latter increase in 11C(R)-PK11195 binding potentially indicates subtle microglial reaction, supporting the hypothesis that microglia reaction underlies early tissue damage preceding demyelination and lesion formation (31). Microglia/macrophages have many different functions and can act in either a beneficial or detrimental fashion in MS pathogenesis. First of all, mononuclear phagocytes are involved in demyelination and phagocytosis of the degraded myelin (32). Inflammation in MS leads to a massive entry of blood-derived macrophages into brain parenchyma. These cells transform into foamy macrophages in the presence of myelin debris and interact with invading T cells (23). At the same time, local inflammatory stimuli lead to a rapid reaction of brain resident microglia and macrophages, which transform into phagocytic cells in the presence of debris. Morphological transformation of myeloid cells also works in reverse: macrophages freshly recruited from the blood stream to the CNS may adapt to the neural environment and undergo remarkable structural remodeling, gradually developing branched processes and transforming into microglia-like ramified cells. Thus, both populations – resident microglia and hematogenous macrophages – contribute to the phagocytic removal of myelin and oligodendrocytes (23). Mononuclear phagocytes are found in most – if not all – MS lesions, and finding myelin degradation products engulfed within tissue macrophages/microglia remains one of the most reliable histological markers of active demyelination (33). Phagocytic activity by macrophages and microglia in MS can be seen as a double-edged sword; on the one hand, it is beneficial by clearing cellular debris, but on other the hand, it is destructive for CNS tissues (34, 35). In addition, microglial/macrophage cells contribute to MS and EAE pathogenesis through antigen presentation, expressing MHC class II and co-stimulatory molecules (CD83/CD40) (23, 36). Microglia express all known TLRs (TLR 1–13) and these receptors are pivotal for the generation of neuro-immune responses (37–40). Microglia/macrophages also promote inflammation and tissue damage (i) by secretion of pro-inflammatory cytokines, reactive oxygen intermediates, and proteinases, (ii) by release of soluble factors that are chemotactic and activate other lymphocytes, and (iii) by physically disrupting the local extracellular environment, thereby facilitating leukocyte influx into the CNS and leading to tissue damage (41). Microglia/macrophages can act as antigen presenting cells and therefore re-prime or reactivate T cells in lesion sites (34, 42). Although the above-mentioned studies emphasize the negative contribution of microglial/macrophage cells in MS or EAE pathology, there is evidence indicating a protective function of these cells in EAE and MS. Indeed, mononuclear phagocytes can inhibit the adaptive immune responses in the CNS, by secreting anti-inflammatory cytokines (IL-10 and TGFβ) or by expressing inhibitory molecules such as PD-L1 (B7-h1) (43). Triggering receptor expressed on myeloid cells-2 (TREM2), a specific membrane-bound receptor involved in reducing inflammation and promoting phagocytosis, is increased in the CSF of both progressive and relapsing–remitting MS patients (24, 41, 44). Microglia/macrophages are also capable of secreting neurotrophic factors such as BDNF, insulin-like growth factor-1 (IGF-1), and neurotrophin 3 (NT3) and thus may contribute in promoting neural survival and neurogenesis (45, 46), although inducing the release of NO by astrocytes (47). Mononuclear phagocytes have been shown to have a beneficial role in EAE, as remyelination was impaired after depletion of macrophages with clodronate liposomes (48). However, the relevance of these findings to human demyelinating diseases is still unclear. Thus, in MS, microglial

cells and macrophages may display both neurodestructive and neuroprotective functions (35). Switching their function from neurodestructive to neuroprotective may be beneficial in preventing chronic demyelination and axonal loss and thus preventing disease progression.

Microvesicles: Novel Biomarkers of CNS Diseases

In multicellular organisms, communication between cells is a fundamental process to guarantee adequate coordination among different cell types within tissues and to exchange information. Classical means of cell communication are represented by three main mechanisms: (i) cell-to-cell contact-dependent signaling, mediated by adhesion molecules and gap junctions; (ii) secretion and diffusion of signaling molecules that can act on a short distance target (paracrine signaling) or on a longer one (endocrine signaling); (iii) synaptic signaling (typical of neurons) in which neurons, through their axons, can reach distant target cells and create with them a junction called "chemical synapse." In addition to these described processes, other mechanisms of cell communication have recently attracted increasing interest: tunneling nanotubes (49) and extracellular vesicles (EVs). Here, we focus on EVs. EVs are spherical membrane vesicles heterogeneous in size (up to 1 μm in diameter) and limited by a lipid bilayer containing hydrophilic soluble components. EVs can form either at the plasma membrane or in the lumen of internal compartments and are secreted into the extracellular space. Irrespective of their origin, these vesicles contain cytosol and have the same membrane topology of parental cells, exposing at their outer surface the extracellular side of the bilayer of donor cells. Because their membrane orientation is the same as that of the donor cell, they can be considered to be miniature versions of the donor cell (50). EVs are thought to function as shuttles for the delivery of cargo between different cells within an organism (51). Indeed, EVs carry receptors, bioactive lipids, proteins, and, most importantly, nucleic acids, such as RNA and microRNA (miRNA); thus, EVs may modify the phenotype and functions of target cells (52). Nowadays, three types of EVs are distinguished unanimously: exosomes, microvesicles (MVs, also called shedding vesicles, ectosomes, shedding MVs, or microparticles), and apoptotic bodies, also called apoptotic blebs or apoptotic vesicles (50, 53, 54) (**Figure 1**). Exosomes are secreted membrane vesicles (approximately 30–120 nm in diameter) formed intracellularly and released from exocytosis of multivesicular bodies (55, 56), whereas apoptotic bodies (approximately 500–4000 nm in diameter) are released by dying/apoptotic cells (57) (**Figure 1**). MVs are heterogeneous membrane vesicles (approximately 200–1500 nm in diameter), which bud directly from the plasma membrane (58) (**Figure 1**). All these different types of vesicles are present simultaneously in the extracellular environment of tissues (**Figure 2**). We here focus on MVs. Upon vesciculation, released MVs can both remain in the extracellular space in close proximity to the cell of origin or diffuse in biological fluids (59). MVs mediate cell-to-cell communication interaction with target cells by different mechanism: (a) stimulation of target cells by acting as signal complex, (b) transfer of surface receptors from one cell to another, (c) delivery of proteins, mRNA, and miRNA, (d) vehicle mechanism to transfer infectious particles (e.g., HIV, prions) (60). Growing evidence indicates that MVs contribute to the pathogenesis of cancer, inflammation, autoimmune, and cardiovascular disease (61). Numbers of MVs in biological fluids seem to correlate with the active phase of many diseases, thus MVs are currently under investigation as possible biomarkers.

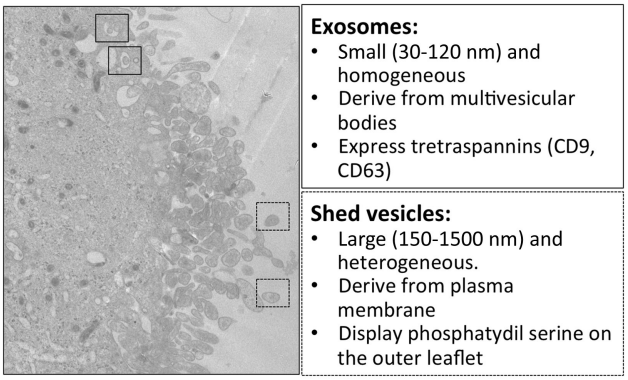

FIGURE 1 | Electron microscopy and main features of microglial exosomes and shed vesicles. Transmission electron microscopy of the human CHME-5 microglial cell line exposed to ATP (500 μM); massive blebbing of the membrane occurs in a short time (5–7 min). In this image, multivesicular bodies containing exosomes are indicated in the solid squares, while released shed vesicles are indicated in dashed squares. Corresponding features are reported in the boxes on the right.

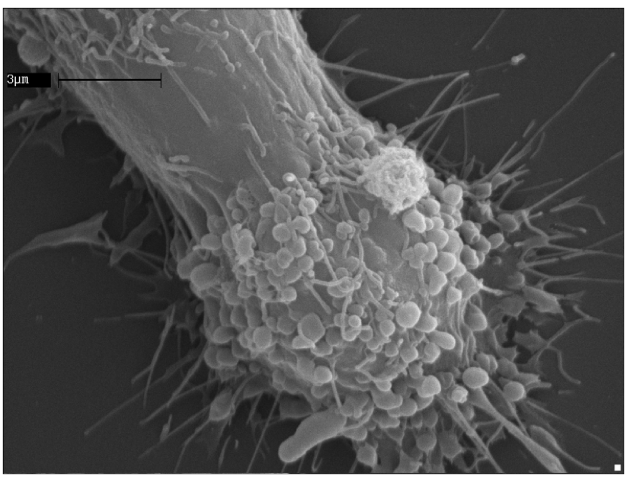

FIGURE 2 | ATP induces extensive blebbing and shedding of myeloid-cell plasma membrane. A human microglia cell of the CHME-5 line exposed to ATP (500 μM); the massive blebbing of the membrane occurs in a short time (5–7 min), witnessing the strength of the connections between the purinergic signaling receptors activation and the cell surface dynamics.

Microvesicles in Multiple Sclerosis

Several studies demonstrate that EVs (both MVs and exosomes) play an active role during the pathogenesis of MS and EAE. MVs from the brain endothelium have been shown to activate both $CD4^+$ and $CD8^+$ T cells toward neural antigens in the absence

of any other stimulatory signal and may represent the potential initial step of brain autoimmunity (62). Increased numbers of MVs have been reported in the blood and in the CSF of MS patients as compared to healthy controls. MVs have been proposed to play a role in inflammatory progression and lesion repair. Injection of microglial MVs into the brain of mice with subclinical EAE recruits inflammatory cells to the injection site (58). However, aSMase deficient mice, which are impaired in MV production in microglia and astrocytes, are largely protected from EAE, although these genetic mutant mice may have defects also in other compartments relevant to the disease. MVs released from BBB-endothelial cells, platelets, leukocytes, myeloid cells (monocytes/macrophages/microglia), and astrocytes, are involved in the pathogenesis of MS (63). The first step is the migration of inflammatory cells through the BBB. Endothelial MVs carry metalloproteases that promote BBB disruption (64) and molecules inducing endothelial activation (65). Endothelial MVs can interact and form complexes with monocytes and activate them (66). Also, activated T cells release MVs containing the chemokine CCL5 and arachidonic acid, which recruite monocytes and up-regulate ICAM-1 on endothelial cells and LFA1 and Mac-1 on monocytes (63, 67). Platelet-derived MVs express on their surface P-selectin, which binds to PSGL-1 and PECAM-1 from lymphocytes by increasing the expression of integrins such as α4β1 (VLA-4) (63). This process promotes the binding of lymphocytes to the endothelium (68) and their transmigration into the CNS. Moreover, together with endothelial-derived MVs, platelet-derived MVs from MS patients have been shown to increase the permeability of endothelial layers *in vitro*, suggesting their involvement in the disruption of the BBB (69). In the CNS compartment, MVs shed by myeloid cells contain components of the inflammasome, such as IL1-β, MHC-II, and others (70).

Since apparently the level of MVs in biological fluids is associated with the activation of cells involved in MS pathogenesis, several authors have proposed them as plausible biomarkers. The inconsistency of results produced so far depends mainly on pre-analytical errors, technological issues related to MVs measurement, ambiguity in EVs definition (MVs vs. exosomes), correlation with clinical and paraclinical parameters such as disease subtype and severity (EDSS), and MRI.

Concerning studies on CSF, Scolding et al. described, for the first time, the presence of oligodendroglial MVs in the CSF of patients with MS (71). More recently, our group revealed the presence of increased levels of myeloid cells-derived MVs ($Ib4^+$) in the CSF of relapsing–remitting MS patients, compared with healthy controls (58). Higher number of CSF MVs was especially associated to acute disease phase, as compared to stable or chronic phases. In fact, MVs counts in the CSF correlate linearly with gad^+ lesions at MRI. Accordingly, in EAE the concentration of CSF MVs perfectly mirrors the course and severity of both relapsing and chronic EAE peaking at onset and during clinical relapses, and decreasing in the chronic phase of the disease. When we investigated MVs as a possible biomarker in MS, based on ROC analysis, we obtained a sensitivity of 85% and specificity of 100% for distinguishing clinically isolated syndrome (CIS) patients from healthy controls, and a sensitivity of 82% and specificity of 82% for differentiating stable (relapse-free patients) from relapsing MS patients (58). Unfortunately, studies of MVs in the CSF of MS patients are difficult to perform, both because of the scarcity of material usually available, and because patients for ethical concerns can not perform serial lumbar punctures to assess MVs' trend over time. For these reasons, many studies have focused on the evaluation of MVs' levels in the peripheral blood, trying to correlate their number with some clinical and instrumental parameters.

$CD31^+$ endothelial MVs, identified in plasma samples by FACS, have been associated to clinical and neuroradiological exacerbation of MS, while $CD51^+$ endothelial MVs have been found elevated in both relapsing and remitting MS patients as compared to controls (65). The same group has confirmed their findings in 2004, further describing that most endothelial MVs can be detected in the blood in the form of conjugates with other cells, especially monocytes (66), while described that, similarly to stroke, platelet-derived MVs, despite elevated in the plasma of MS patients as compared to controls, display a reduced discriminating power between health and disease (68). Jimenez et al. (72) reported an increase of $CD54^+$ and $CD62E^+$ endothelial MVs in the plasma of MS patients during relapse compared to remission. Sáenz-Cuesta et al. (73) demonstrated a significant difference also in $CD61^+$ (platelet marker), $CD45^+$ (lymphocyte marker), and $CD14^+$ (monocyte marker) MVs counts in samples from MS patients compared to those from healthy controls. MVs were especially high in relapsing–remitting patients, while secondary progressive MS patients were similar to healthy controls. Plasma MVs levels in this work appear to reflect short-term active inflammation rather than disease severity, as measured by EDSS, or disease duration or patients age (73).

Considering MVs as biomarkers of therapeutic efficacy in MS, Jimenez et al. (72) report that IFN-β 1b reduces the release of endothelial MVs induced by plasma from MS patients. IFN-β 1b also reduces monocyte–endothelial MVs complex formation and transendothelial migration *in vitro* (72). Sheremata et al. (74) report the ability of IFN-beta1a to reduce the number of $CD31^+$ endothelial MVs in plasma of relapsing–remitting MS patients as early as three months after treatment initiation without, however, any correlation with MRI activity. Lowery-Nordberg et al. performed a prospective study, measuring changes in plasma of $CD31^+$, $CD146^+$, and $CD54/ICAM\text{-}1^+$ endothelial MVs in 16 patients with RR-MS before and after 3, 6, and 12 months of therapy with interferonbeta1a (Rebif44®). They found that plasma levels of $CD31^+$, and $CD54^+$ – and not $CD146^+$ – endothelial MVs were significantly reduced by treatment with IFNβ. Moreover, they demonstrated a significant association between the decrease in plasma levels of MVs and the decrease in the number and volume of contrast enhancing T1-weigthed MRI lesions (75). On the contrary, in a recent study measuring plasma platelet MVs, lymphocyte MVs, and monocyte MVs, Sáenz-Cuesta et al. (73) reported, using flow cytometry (probably focusing on MVs), higher counts of all three MVs subtypes in IFN-β and natalizumab-treated patients (73). Dawson et al. demonstrated that fingolimod inhibits aSMase (76), the enzyme that controls MVs production (17). In our work (58), we hypothesized that fingolimod might inhibit myeloid cells-derived MVs shedding from reactive microglia. Indeed, EAE mice

treated with fingolimod displayed a reduction of CSF myeloid MVs to baseline levels. Through this mechanism, fingolimod may inhibit the spreading of inflammatory signals throughout the brain parenchima (58).

Conclusion

There is still incomplete information on the role of microvesicles in MS, but available evidence points to a relevant role, both in spreading pro-inflammatory signals and in altering neuronal functions. The potentially relevant role in the pathogenesis of the disease, underlines how microvesicles, especially those released by microglia/macrophages, may represent precious biomarkers, although for the moment they only can indicate, for example, the presence of microglial reaction, but are not linked to a specific disease. Involvement in pathogenic mechanisms may suggest also microvesicles as possible therapeutic targets. The development of adequate technology for the detection and analysis of microvesicles will provide in the near future the answer to the questions posed in this review and reveal if new and valuable information on MS is indeed enveloped in these microscopic nanoparticles.

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MINI REVIEW
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The neurophysiologist perspective into MS plasticity

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Multiple sclerosis (MS) is a frequent, highly debilitating inflammatory demyelinating disease, starting to manifest in early adulthood and presenting a wide variety of symptoms, which are often resistant to pharmacological treatments. Cortical dysfunctions have been demonstrated to be key components of MS condition, and plasticity of the corticospinal motor system is highly involved in major MS symptoms, such as fatigue, spasticity, or pain. Cortical dysfunction in MS can be studied with neurophysiological tools, such as electroencephalography (EEG) and related techniques (evoked potentials) or transcranial magnetic stimulation (TMS). These techniques are now widely used to provide essential elements of MS diagnosis and can also be used to modulate plasticity. Indeed, the recent development of non-invasive brain stimulation techniques able to induce cortical plasticity, such as repetitive TMS or transcranial direct current stimulation, has brought promising results as add-on treatments. In this review, we will focus on the use of these tools (EEG and TMS) to study plasticity in MS and on the major techniques used to modulate plasticity in MS.

Keywords: multiple sclerosis, transcranial magnetic stimulation, non-invasive brain stimulation, electroencephalography, plasticity

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Introduction

Multiple sclerosis (MS) is usually described as an inflammatory demyelinating disease involving mainly the white matter. However, axonal loss (1) and cortical damage (2–6) are also important clinical features of the disease. The first demonstration of cortical involvement was reported in the 1980s, showing losses of orientation-specific contrast sensitivity and abnormal visual evoked potentials (VEPs) in MS (7, 8). The role of cortical damage in the disease course and clinical deficits has been since then further investigated and plasticity of the corticospinal motor system has been identified as a key component of major debilitating symptoms, such as fatiguability or spasticity (9–19).

Neurophysiological examinations are thus of primary importance in the clinical care of MS. They allow both the investigation of corticospinal sensorimotor mechanisms involved in the disease, using electroencephalography (EEG), electromyography (EMG), and transcranial magnetic stimulation (TMS), and also allow clinicians to directly act on deficient cortical circuits to improve subjects' condition, using non-invasive brain stimulation (NIBS), such as repetitive TMS (rTMS), theta burst stimulation, transcranial direct current stimulation (tDCS), or using peripheral nerve stimulation, such as transcutaneous electrical nerve stimulation (TENS).

In this review, we will focus on the importance of neurophysiological tools to study and modulate plasticity in MS to help treat major symptoms of the disease.

Exploring Cortical Plasticity in MS

Event-Related EEG Oscillations

EEG represents an important exploratory tool in clinical neurophysiology practice in general and in particular in the care of MS, especially using multimodal evoked potentials (EPs), such as somatosensory evoked potentials (SEPs), auditory evoked potentials (AEPs), or VEPs. These measurements allow indeed a quantitative assessment of the system function targeted by the examination.

Apart from the evoked activity, cortico-thalamo-cortical loops can be studied using induced EEG activity in relation to internal or external events. In particular, event-related desynchronization/synchronization (ERD/ERS) of the sensorimotor mu (8–12 Hz) and beta (13–25 Hz) rhythms is strongly related to the cortical motor control (20–22). ERD represents an attenuation of the EEG signal amplitude. Mu and beta ERD, predominating over the sensorimotor cortical areas contralateral to movement, initiate about 1.5 s before movement onset and are maximal at movement onset. Mu/beta ERD, usually observed before and during self-paced voluntary movements (23, 24), reaction time paradigms (25), passive movements (26, 27), or motor imagery (28), reflect the activation of cortical motor/premotor areas involved in motor planning. Beta ERS corresponds to a brisk, intense amplitude increase following movement termination, observed in the beta band. Beta ERS would be related to a post-event inhibitory period strongly related to sensory reafferentation (29–32). The mu/beta ERD/ERS analysis is thus a robust method to study the cortical processing of motor control.

Beta ERD was abnormally increased in the fronto-central regions in fatigued MS subjects, compared to non-fatigued subjects or controls (11). The study involved non-disabled subjects [with score $\leq$1.5 according to the Expanded Disability Status Scale (EDSS)]. Non-fatigued subjects did not show abnormal mu/beta ERD/ERS. Conversely, beta ERS was significantly lower in fatigued MS participants over fronto-central areas. These abnormal ERD/ERS patterns were significantly correlated with the amount of fatigue. Such increased beta ERD and decreased beta ERS reflected an increased cortico-thalamo-cortical activity in fatigued MS subjects, consistent with the central origin of fatigue in MS, and suggesting an over-activity of frontal structures (probably the supplementary motor area). In another study involving more severe MS participants, the authors showed a significant correlation between mu ERD onset and T1/T2 total lesion volume, the more severe subjects having higher lesion loads and more delayed mu ERD (33). These results imply that, with the progression of the disease, the extent of brain lesion load affects cortico-cortical and cortico-subcortical activity related to motor planning.

Long-Latency Reflexes

Long-latency reflexes (LLRs) are muscular responses elicited by electrical stimulations of mixed nerves during slight contraction of the targeted muscle. In particular, LLR-II would be the most reliable (34) and would represent a transcortical reflex (35–40). LLR-II represents an important neurophysiological tool to study simultaneously the sensory-motor corticospinal tracts and intracortical circuits. There is a strong correlation between LLR-II latencies and the sum of latencies of the N20 SEP and motor-evoked potential (MEP) evoked by TMS, suggesting that the three phenomena (LLR-II, SEP, and MEP) are essentially conducted along the same fibers (39). The cortical relay time (CRT) can be obtained by subtracting the sum of the latencies of N20 and of MEP to the LLR-II latency. CRT is usually consistent with polysynaptic or oligosynaptic intracortical transmission (41). Delayed or absent LLRs in MS were revealed in the early 90s, demonstrating the relevance of studying simultaneously LLRs and SEPs to evaluate afferent and efferent pathways in MS (42, 43). More specifically, the CRT was reported prolonged in people with definite MS (44, 45). Tataroglu and colleagues demonstrated also prolonged LLR-II, N20 SEP, and MEP latencies in MS. The CRT was not correlated with the clinical form of the disease or with its duration, in contrast to the other measurements. Bonfiglio and colleagues showed only weak differences between people with MS and controls in terms of afferent (N20) or efferent (MEP) conduction times, but demonstrated strong differences of LLR latencies between both groups (45). Moreover, CRT was greatly prolonged in MS compared to controls, and not only in subjects who had severe slowing of central sensory and/or motor conduction. The CRT increase did not correlate with disease duration. This study showed how slowing of intracortical sensorimotor circuits greatly contributes to the delayed LLR-II latencies in MS. LLR recording may thus be useful to detect dysfunctions of the intracortical sensorimotor pathway in MS. Attention can be directed on the fact that these intracortical sensorimotor disorders are present in most of MS subjects, independently from the disease duration and even in non-severe forms.

Transcranial Magnetic Stimulation

TMS was initially used in MS to measure central motor conduction time (CMCT) to evaluate the effects of demyelination on neuronal conduction. CMCT is indeed significantly prolonged in MS (46–48). Moreover, depending on the paradigm used, single or paired-pulse TMS allows the investigation of the whole corticospinal tract integrity, including intracortical excitability. Such paradigms have been used in MS and showed increased resting motor threshold (RMT), or absent MEPs in most of subjects, demonstrating abnormal excitability of pyramidal neuron membrane (46, 47, 49). Increased threshold and reduced cortical silent period (CSP, a measure of intracortical GABAb transmission) were demonstrated characteristic of "relapsing" subjects. These participants also lacked short-interval intracortical inhibition (SICI), a measurement of intracortical GABA-a interneuronal transmission (50–52). Normal threshold and prolonged CSP were observed in the "remitting" phase (53). Strong correlations were shown between hand motor function (measured with the Purdue Pegboard score) and RMT, MEP amplitude/latencies in relapsing-remitting MS (54). Relapsing-remitting subjects had lower RMT and higher MEP amplitudes than subjects with secondary progressive MS, who had significantly higher RMT and smaller MEPs than controls (48, 55). Secondary progressive MS also showed lower amounts of SICI than relapsing-remitting form and than healthy controls, directly demonstrating an alteration of the intracortical GABAergic transmission in MS (55). These TMS

measures correlated with EDSS scores, revealing normal TMS measures in subjects with lower EDSS scores and abnormal corticospinal excitability in people with higher EDSS scores (i.e., higher disability), demonstrating that TMS evaluation is of importance in quantifying MS disease severity (48, 55, 56). Also, changes in the balance of intracortical excitation and inhibition, favoring excitation, have been reported using paired-pulse TMS after high-dose corticosteroids in relation to a relapse (57). More studies are needed in order to ascertain the respective role of lesion location (e.g., motor or extra-motor relapse), of spontaneous recovery and of treatment administration.

TMS can also be used as a non-invasive tool able to interfere temporarily with a specific cortical activity in order to investigate its particular role. To this aim, single pulse TMS has been used to investigate the role of ipsilateral motor/premotor cortex hyperactivity during a simple reaction time task in MS (58). The authors applied a suprathreshold TMS pulse targeting, in different sessions, the contralateral and ipsilateral hand motor cortices or the ipsilateral dorsal premotor cortex during a simple reaction time task. They showed that the concomitant stimulation of the contralateral primary motor cortex increased significantly the reaction times in both people with MS and controls. Conversely, stimulation of the ipsilateral motor/premotor cortex increased reaction times only in MS, and not in controls. These changes in reaction times, however, did not correlate with hand motor function tests or with the total brain lesion load. The authors concluded thus that the ipsilateral hyperactivity might be a "functionally relevant, yet limited adaptive response to chronic brain injury in MS patients."

Modulating Cortical Plasticity in MS

Non-Invasive Brain Stimulation

Non-invasive brain stimulation techniques are relatively new tools for modulating cortical excitability to provide symptomatic treatments in a large range of neurologic and psychiatric diseases. Among them, rTMS and tDCS have been widely studied and proven effective in conditions, such as Parkinson's disease, stroke, or dystonia (59–62). Since these techniques have been particularly applied in the field of neurorehabilitation, a special interest rose to improve specific dysfunctions of subjects with MS.

Cortical plasticity can indeed by induced in MS. Subjects with moderately severe stable MS showed the same rapid-onset motor plasticity than healthy subjects, despite motor impairment and central nervous system injuries (63). The authors used paired-associative stimulation (PAS), a NIBS protocol modeling long-term synaptic potentiation (LTP) (64), combining repetitive electric nerve stimulation with TMS of the contralateral motor cortex. In both groups (MS and controls), PAS induced an increase in corticospinal excitability and improved motor learning performances equally in subjects with MS and controls. On the other hand, PAS-induced plasticity was reduced in relapsing-remitting MS subjects suffering incomplete or absent recovery (65). The authors showed that PAS-induced plasticity (measured with MEPs and SEPs amplitude and latencies) and age could contribute to predict symptom recovery after a relapse.

One of the first applications of NIBS in MS has been to reduce spasticity. Indeed, rTMS is able to modulate the presynaptic inhibition of the soleus Ia afferents mediating the stretch reflex (66, 67). Centonze and colleagues first applied low (inhibitory) and high (excitatory) frequency rTMS over the leg primary motor cortex in 19 subjects with remitting MS and showed that a single session of high-frequency rTMS (5 Hz) could reduce the amplitude of the H/M ratio of the soleus H reflex and increase MEP amplitude (18). Two consecutive weeks of 5 Hz rTMS treatment decreased H/M amplitude ratio as well as spasticity [directly measured on Modified Ashworth Scale (MAS) mean score], up to 1 week after the end of treatment (18). In a pilot study using the H-coil, which is able to deliver a wider and deeper magnetic field than the regular focal coils without the need to increase the stimulation intensity (68), 3 weeks of treatment with 20 Hz rTMS over the leg area of subjects with progressive MS could improve walking and reduce spasticity more than rehabilitation alone (69). Intermittent theta burst stimulation (iTBS), which represents another way of using high-frequency rTMS to increase corticospinal excitability (70), has also been reported to reduce spasticity (MAS scores and H/M amplitude ratio) in the remitting phase of MS for up to 2 weeks after the end of the 2-week stimulation protocol (71, 72). The effects of iTBS, combined with exercise therapy, were potentiated with respect to the two treatments alone, suggesting the association of these two rehabilitation methods as a promising strategy (72). Conversely, iTBS-induced LTP was reported absent in subjects with primary progressive MS, who also presented lesser amounts of platelet-derived growth factor (73), a molecule considered neuroprotective (74) and favoring LTP (75).

NIBS techniques have also been used to treat fatigue in MS. Indeed, cortical involvement in fatigue mechanisms was demonstrated through impaired intracortical inhibition (13), dysfunction of inhibitory mechanisms engaged after movement termination (11, 76), in line with neuroimaging evidence (6). Positron emission tomography at rest revealed metabolic abnormalities of frontal cortex and basal ganglia (77) and functional magnetic resonance imaging during motor activity showed dysfunction of cortical and subcortical areas involved in motor planning (12). tDCS, another NIBS method for inducing long-term modulation of cortical excitability (78, 79), has been recently explored to reduce fatigue in MS. Anodal (excitatory) tDCS of the motor cortex applied for 5 days in 25 MS subjects (22 relapsing-remitting) could improve fatigue impact scale (FIS) scores by about 30% in 65% of participants (80). These benefits were still present 3 weeks after the end of treatment. More recently, 5 days of bilateral anodal tDCS over the primary somatosensory cortical areas were able to decrease fatigue (modified FIS scores) in 10 MS subjects (81). Anodal tDCS over the somatosensory cortex could also reduce tactile sensory deficits by improving discriminatory thresholds at the grating orientation task and increasing the visual analog scale (VAS) for sensory scores in 20 remitting subjects (82).

Another application of NIBS in MS has been neuropathic pain. Central neuropathic pain is influenced by functional changes at the supra-spinal level, in various components involved in pain perception. In particular, the thalamic nuclei, limbic system, sensorimotor, and insular cortices function in a hyperactivated state. A lack of intracortical inhibition would also be involved in central

neuropathic pain (83). Based on these observations, epidural and transcranial stimulation of the motor cortex, modulating pain perception through indirect neural networks, have been applied in humans for the treatment of drug-resistant neuropathic pain (84). Five days of anodal tDCS over the primary motor cortex reduced pain (assessed by VAS for pain and McGill questionnaire) and improved quality of life in 19 remitting MS subjects (85), up to 3 weeks after the end of treatment.

These studies demonstrated that neuromodulation of cortical plasticity using NIBS can have diverse applications to benefit people with MS. NIBS over M1 might reduce spasticity and neuropathic pain through an increase in corticospinal excitability (18, 70, 86), while the positive effects on fatigue might depend on cortico-cortical and/or cortico-subcortical mechanisms (80, 81).

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation is used in the treatment of acute or chronic pain symptoms (87). TENS usually consists on the use of small battery-powered devices delivering alternative current through cutaneous electrodes placed near the painful area. TENS efficacy depends on the intensity and frequency of stimulation. TENS activates large diameter afferent fibers, which in the central nervous system may activate descending inhibitory circuits reducing hyperalgesia (88, 89). In animal models, low and high-frequency TENS reduce dorsal horn neuronal activity (90–93). High-frequency TENS also reduces central neuronal sensitization and release of glutamate and substance P in the spinal chord dorsal horn in preclinical models of inflammation (94, 95). In MS, TENS has been reported to reduce spasticity, pain, and muscle spasms (96, 97). Recently, a TMS study investigated the effects of a 3-week TENS treatment on cortical map representation (98). TENS, applied on the median nerve region (thenar eminence) of the most impaired hand 1 h a day for 3 weeks, was associated with decreased cortical map area of hand muscle representation, without modifying RMT or MEP amplitude. These findings were interpreted as reflecting reorganization in the cortical motor representation rather than a temporary decline in corticospinal excitability, suggesting that TENS can induce cortical plastic changes in MS.

Conclusion

A variety of neurophysiology tools can significantly help in the investigation and reinforcement of neuroplasticity in MS. Importantly, the development of NIBS techniques is bringing new possibilities for add-on treatment strategies. Thus, the combination of these tools could help personalize treatments for people with MS.

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Brain plasticity effects of neuromodulation against multiple sclerosis fatigue

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Rationale: We recently reported on the efficacy of a personalized transcranial direct current stimulation (tDCS) treatment in reducing multiple sclerosis (MS) fatigue. The result supports the notion that interventions targeted at modifying abnormal excitability within the sensorimotor network could represent valid non-pharmacological treatments.

Objective: The present work aimed at assessing whether the mentioned intervention also induces changes in the excitability of sensorimotor cortical areas.

Method: Two separate groups of fatigued MS patients were given a 5-day tDCS treatments targeting, respectively, the whole body somatosensory areas ($S1_{wb}$) and the hand sensorimotor areas ($SM1_{hand}$). The study had a double blind, sham-controlled, randomized, cross-over (Real vs. Sham) design. Before and after each treatment, we measured fatigue levels (by the modified fatigue impact scale, mFIS), motor evoked potentials (MEPs) in response to transcranial magnetic stimulation and somatosensory evoked potentials (SEPs) in response to median nerve stimulation. We took MEPs and SEPs as measures of the excitability of the primary motor area (M1) and the primary somatosensory area (S1), respectively.

Results: The Real $S1_{wb}$ treatment produced a 27% reduction of the mFIS baseline level, while the $SM1_{hand}$ treatment showed no difference between Real and Sham stimulations. M1 excitability increased on average 6% of the baseline in the $S1_{wb}$ group and 40% in the $SM1_{hand}$ group. Observed SEP changes were not significant and we found no association between M1 excitability changes and mFIS decrease.

Conclusion: The tDCS treatment was more effective against MS fatigue when the electrode was focused on the bilateral whole body somatosensory area. Changes in S1 and M1 excitability did not correlate with symptoms amelioration.

Significance: The neuromodulation treatment that proved effective against MS fatigue induced only minor variations of the motor cortex excitability, not enough to explain the beneficial effects of the intervention.

Keywords: fatigue in multiple sclerosis, electroencephalography, transcranial magnetic stimulation, transcranial direct current stimulation, magnetic resonance imaging, electrode personalization

Introduction

Fatigue is defined as "a feeling of insufficient physical and/or mental energies interfering with the usual and desired activities" (1). It is a common and highly disabling symptom in patients affected by multiple sclerosis (MS) even when other symptoms remain mild (2).

Involvement of the Motor Control System in MS Fatigue

To date, there is no clear evidence pointing at a single factor causing MS fatigue and fatigue complaints appear completely unrelated to both clinical variables, such as type of MS, level of disability, or disease duration, and demographic ones, such as age, gender, and education level (3). Although peripheral conditions, such as muscle weakness, may play a role, there are clear indications that much of MS fatigue has a central origin, most likely being the consequence of a failing central motor transmission to spinal alpha motor neurons (4).

tDCS Treatment Targeting "Whole Body S1" vs. "Hand SM1"

A few years ago, Cogiamanian obtained an increase of endurance against fatigue in healthy subjects by submitting them to a transcranial direct current stimulation (tDCS) (5). Recently, we applied Cogiamanian's treatment to fatigued MS patients (6) obtaining a significant amelioration of their symptoms. In the present study, we tested two variations of Cogiamanian's protocol on two distinct subgroups of fatigued MS patients. We submitted the first subgroup to Cogiamanian's same treatment only replacing the original mono-hemispheric with a bihemispheric stimulation (we will call this treatment $SM1_{hand}$).

It is known that fatigued MS patients show a much higher excitability of their primary motor area (M1) than non-fatigued patients and healthy subjects. This phenomenon has been attributed to a failure of intracortical inhibition (ICI) in frontal and M1 areas, both before and after fatiguing exercises (4). Furthermore, structural and functional data report a parietal involvement in MS fatigue symptoms (7–9), with indications of a reduced primary somatosensory area (S1) excitability (10, 11), and tDCS has been reported to enhance parieto-frontal projections (12). Also, in previous works of ours, we noticed signs of impaired communication between S1 and M1 (13).

Consequently, on the base of the above considerations, for the second subgroup, we modified Cogiamanian's treatment to selectively direct our neuromodulation on bihemispheric whole body S1, avoiding further direct enhancement of M1 excitability (14). Cogiamanian and coworkers assessed fatigue in hand movements and stimulated the hand section of SM1 representation (5). We considered that in MS patients, the lower limbs are also primarily involved and there are no reasons to limit neuromodulation to only the section of S1 devoted to hand representation. Thus, we treated the second subgroup with a tDCS on bilateral whole body S1 (we will call this treatment $S1_{wb}$).

Aim

Within this theoretical frame, our present aim was to test whether a tDCS treatment, which decreases MS fatigue, induces changes in brain excitability. In particular, we intended to quantify the effects induced within M1 via transcranial magnetic stimulation (TMS)-evoked motor evoked potentials (MEPs) (15) and in S1 via median nerve (MN) evoked somatosensory evoked potentials (SEPs).

Materials and Methods

The protocol was approved by the Ethics Committee of the "S. Giovanni Calibita" Fatebenefratelli Hospital in Rome and by Ethics Committee of Università degli Studi di Milano, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena.

Study Design

Both our studies ($S1_{wb}$ and $SM1_{hand}$ treatments) followed a double blind, sham-controlled, randomized, cross-over design (Sham/Real, Real/Sham). Patient remained blind to whether they would receive a real or a sham treatment. Patients were asked to fill out the modified fatigue impact scale (mFIS) form to score their level of fatigue. We will refer to the week before the first tDCS treatment as T0 (baseline) and to at least 4 h after the last tDCS treatment as T1. We collected electroencephalographic (EEG) and TMS sessions and mFIS scores at T0 and T1.

Sample Size Estimate

We calculated the sample size using the repeatability of mFIS scores before neuromodulation treatments started. In 10 individuals with mild MS, we collected mFIS twice, 1 week apart. The average mFIS pre–post score difference was 0.1 ± 1.9, and the Intra-Class Correlation indicated a very high agreement (ICC = 0.96; $p < 0.001$). According to our previous study (6), the variability of changes after stimulation was quite larger (21.1% after real, 16.9% after sham). In order to assume the "worst" yet more realistic scenario, we did not lean on homoscedasticity and assumed both such variability values, distinguishing real and sham variances of pre–post-stimulation changes. In Tecchio et al. (6), we observed a 27% improvement after real and 7% improvement after sham treatment. To recognize as significant (alpha level = 0.05), a 20% difference between Real and Sham treatments, a sample size of 10 cases will provide a power of 90%. Notably, biomedical literature considers a 25% improvement (ere expected for Real stimulation) as a suitable threshold of clinical relevance (16) and here would

correspond to a decrease of 12 mFIS points for a severely fatigued patient with 48 at baseline.

Participants

We recruited 21 relapsing-remitting (RR) MS patients (17) experiencing fatigue [physical items mFIS score >15, Ref. (18)]. Inclusion criteria were as follows: mild physical disability [expanded disability status scale, EDDS (19) cut-off score of ≤3], absence of depression (no pharmacological treatment), absence of clinical relapse, or radiological evidence of disease activity over the last 3 months. Exclusion criteria were as follows: use of symptomatic drugs, which may affect the level of fatigue, depression, and anxiety within the past 3 months (20), epilepsy or other central/peripheral nervous system comorbidities and any systemic conditions, which may cause fatigue (e.g., anemia and pregnancy). All patients underwent brain magnetic resonance imaging (MRI) for exclusion criteria assessment. In addition, a detailed clinical history was collected including active disease modifying therapy (DMT), disease duration, annual relapse rate, and depression level (Beck depression inventory, BDI). Fine hand motor control was evaluated by nine hole peg test (9HPT) scores collected separately for left and right sides.

MRI Exam and Measure Estimate

Image Acquisition

In each patient undergoing $S1_{wb}$ treatment, brain imaging was performed by an Achieva 1.5-T scanner (Philips Medical Systems, Best, The Netherlands), with 33 mT/m gradients, online 2D/3D geometric distortion correction, and an 8-channels head Phased-Array coil with parallel imaging capabilities (SENSE). All sequences were acquired with contiguous slices and full brain coverage.

Exclusion criteria (no active lesions) were assessed based on T1-Spin Echo images before and 5 min after intravenous injection of a contrast agent. Lesions estimates were based on T2 Dual Echo images (see: column 2 of Attachment 2) and 3D-FLAIR (see: column 4 of Attachment 2).

T1-3D Fast Field Echo sequences with full brain coverage (MPRAGE, TR/TE/FA = 8.6 ms/4 ms/8°; 170 contiguous sagittal slices 1.2 mm thick without gap, mtx1922) were used for the 3D reconstruction of the brain structure in order to personalize the tDCS electrode.

Image Post-Processing Computations

Lesion load

A semi-automated region of interest (ROI) approach was used to trace hyperintense lesions in the white matter (WM) on T2-weighted images, following strategies previously described [Ref. (11); Jim 5.0, Xinapse Systems Ltd., Leicester, UK, Attachment 3]. ROIs were identified by consensus of two investigators (Giancarlo Zito and D. Lupoi) blind to patients' clinical data. The total lesion volume (TLV) was computed. Lesion relative fraction (LrF) was computed as the ratio of the TLV over the WM volume in order to normalize for inter-subject head volume variability.

Whole Body S1 Personalized Electrode Shaping and Positioning

Personalized Electrode Shaping

A few days before the experimental session, each subject underwent a structural brain MRI exam with a 1.5-T scanner (Achieva, Philips Medical Systems, Best, Netherlands; MPRAGE contiguous sagittal slices with full brain coverage). MRI data were elaborated with SofTaxic Neuronavigation System ver. 2.0 (www.softaxic.com, E.M.S., Bologna, Italy), which delivered the volumetric reconstruction of the individual brains and the cortical folders. The stereotaxic procedure for the personalization of each electrode included the following steps [**Figure 1**; (14)]: (1) the line of the central sulcus shown by the navigator is manually transferred onto a paper sheet firmly fixed onto the patient's scalp; (2) on paper, 2 cm-long segments are drawn perpendicularly from a number of equidistant points of the central sulcus line in the anterior direction. The number of equidistant points is chosen to obtain a total electrode surface of 35 cm^2, which the literature widely reports as the recommended size for a direct current intensity of 1.5 mA. (3) The shape obtained on paper is transferred onto a commercial band of conductive silicone. The latter is 0.2 mm thick and has a 1 mm diameter channel running along its length. The electrode is manually cut along the contour, making sure that the channel remains roughly at the center of the band's length. (4) A standard electric wire, which will deliver the 1.5 mA direct current, is finally placed inside the channel.

Following the SofTaxic navigator, the electrode was positioned 1.5 cm posterior and 0.5 cm anterior to the central sulcus, centered on the nasion-inion line. Cathode electrode (6 cm × 14 cm) was

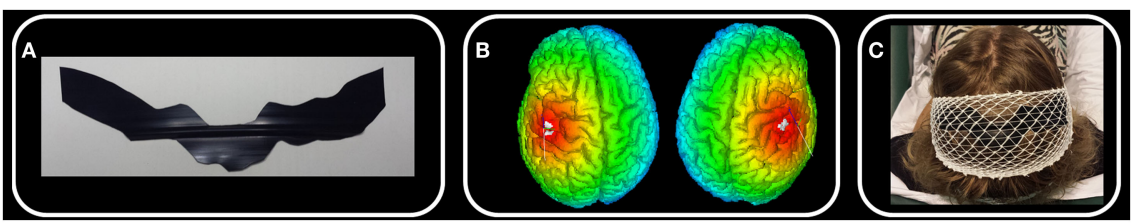

FIGURE 1 | Whole body S1 personalized electrode. In one exemplificative subject, we schematize the main steps of electrode personalization [Ref. (14), see Materials and Methods). **(A)** After drawing the left and right central sulci using SoftTaxic software from individual 3D MRI, we fit this line by 2 cm wide parallelograms and we cut the electrode from a conductive silicon band. **(B)** We position the personalized stimulating electrode by proper neuronavigation procedure along the central sulcus with the center of the electrode crossing the nasion-inion line. **(C)** $S1_{wb}$ personalized electrode and the cathode electrode positioned on Oz.

positioned on Oz. Contact with the subject's head was facilitated by a conductive gel and an elastic cotton net maintained the electrodes stable along the entire session (**Figure 1**).

Transcranial Direct Current Stimulation (5-Day Treatment)

Transcranial direct current stimulation was delivered by an electrical stimulator through a constant current unit and an isolation unit [SM1 (21); S1-Eldith Stimulator by NeuroConn, Ilmenau, Germany]. Anode electrode was positioned as described above. Cathode electrode was under the chin for the SM1 stimulation and on Oz for the S1 stimulation.

The 1.5-mA constant current was applied for 15 min once a day for five consecutive days, according to previous studies against pain (22, 23). In particular, a 1.5-mA current strength produces a current density of about 0.04 mA/cm^2 for the anode electrode of 35 cm^2 (5, 24), which is well below safety thresholds. Cathode electrode size was of 84 cm^2, resulting in a current density of 0.02 mA/cm^2 under this electrode, corresponding to a non-effect current density in this reference region (25, 26). Impedances were below 10 kΩ throughout the stimulations. Sham condition consisted of 4 s of active stimulation at the beginning and at the end of each day's 15-min stimulation. At debriefing, no subject reported to feel any difference across tCSs.

Transcranial Magnetic Stimulation to Probe Cortical Excitability Changes in M1

Single-pulse TMS was performed through a standard focal coil (diameter of each wing 70 mm) connected with a Bistim 200 module (The Magstim Company Ltd., Whitland, UK). We recorded TMS MEPs from left and right *opponens pollicis* (OP) by surface electrodes in a belly tendon montage (2.5 cm apart). Following international standards, we identified the "hot-spot" of the right OP muscle and the corresponding resting motor threshold (RMT) (27, 28). Thereafter, we maintained the coil position – digitized and monitored throughout the whole session by the SofTaxic neuronavigator – by means of a support arm (**Figure 2A**).

Transcranial magnetic stimulation intensity was settled at 120% RMT and 20 MEPs were then collected in complete relaxation while TMS was delivered with an inter-stimulus interval randomly ranging between 5 and 7 s. The whole procedure was repeated in the other hemisphere to obtain left OP motor cortical representation.

Electroencephalographic Study to Probe Cortical Excitability Changes in S1

Electrophysiological Data Recording

Electroencephalographic signals were recorded with a 64-channel actiChamp System (Brain Products GmbH, Gilching, Germany, **Figure 2B**). The montage included Fz derivation for reference and FPz for ground. EEG signals were sampled at 5 kHz and a preconditioning 0.1–1500 Hz bandpass filtering was applied.

Median Nerve Stimulation

All subjects sat comfortably on an armchair during the experiment. In order to induce somatosensory evoked responses following a painless thumb twitch, their MN was stimulated at the wrist with a constant current electrical stimulator (Model DS3, Digitimer Ltd., Hertfordshire, UK), using standard parameters (cathode proximal, 250 ms inter-stimulus interval, 0.2 ms duration, above motor threshold intensity).

Left and right MNs were separately stimulated for 5.5 min, totaling about 1300 artifact-free trials, which were stored for off-line analysis. The SEP epochs ranged from 10 ms pre to 100 ms post-stimulus. Epochs whose voltage amplitudes exceeded ±100 μV at the EOG electrode as well as those containing saturating artifacts were rejected.

All amplitude values referred to the 5–10 ms post-stimulus interval. The amplitude of the N20 component was measured as the first negative peak between 18 and 23 ms. The N20–P25 complex was determined as the difference between the N20 peak and the subsequent positivity peak (P25), occurring at a latency of around 23–29 ms.

For purposes of the present study, we used the typical bipolar derivation used to assess SEPs [C3–C4, Ref. (29)].

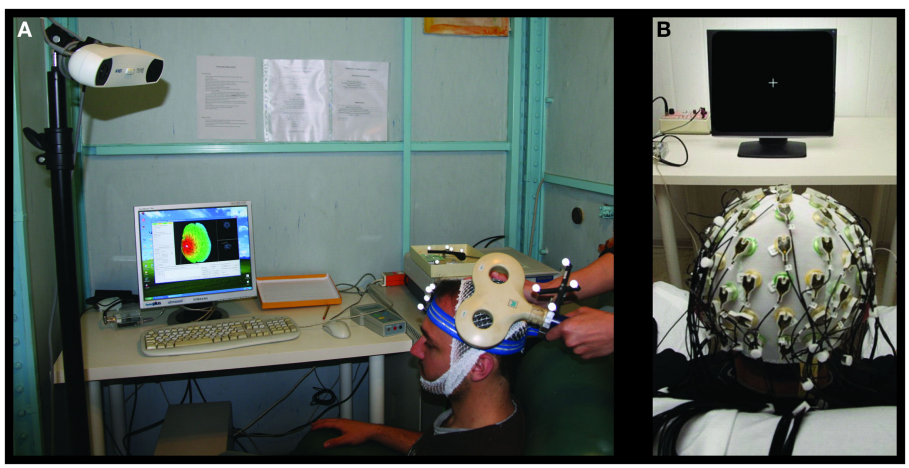

FIGURE 2 | Transcranial magnetic stimulation and EEG settings for brain plasticity assessment. Experimental settings for the MEP **(A)** and SEP **(B)** recordings.

Statistical Analysis

After checking the distribution of MEP and SEP amplitudes (as tested by Shapiro–Wilk test), we applied, when necessary, suitable transformations in order to achieve a better approximation to gaussianity and a good control of outliers.

To test the effects of the 5-day tDCS on MFIS, MEP, and SEP variables, analyses of variance (ANOVA) for repeated measures were performed with *Stimulation* (Real, Sham) and *Treatment* (pre-, post-tDCS treatment) as within-subjects factors. Within-subjects factor *Hemisphere* (Left, Right) was included for MEP and SEP, which had been collected bilaterally since we performed a bilateral stimulation. A similar approach was used for the effects on fine hand motor control measure, with the 9HPT submitted to the ANOVA with *tDCS Intervention* (Pre, Post), *Stimulation* (Real, Sham), and *Hand* (Right, Left) within-subjects factors. We performed separate ANOVA designs in the two patients' subgroups stimulated on bilateral $S1_{wb}$ or $SM1_{hand}$. Significance threshold was set to 0.050 and we reported trends for $p < 0.100$.

Results

The 21 patient cohorts presented a mild clinical picture in accordance to the inclusion criteria (**Table 1**). The two electrode-dependent subgroups displayed homogenous clinical features (**Table 1**).

Fatigue Levels

Whole Body S1 Stimulation ($S1_{wb}$)

Analyses of variance indicated that mFIS changes were related to the type of stimulation (Real or Sham) when the bilateral personalized $S1_{wb}$ electrode was used [*Stimulation* × *Treatment* interaction $F(1,8) = 9.692$, $p = 0.014$, (6), **Table 2**]. Fatigue resulted reduced after real stimulation (*post hoc* comparison $p = 0.002$, 31.0 ± 12.0 post- vs. 42.1 ± 7.9 pre-stimulation), whereas there were no changes after the sham stimulation [*post hoc* comparison $p = 0.901$, 34.8 ± 10.4 post- vs. 37.2 ± 7.0 pre-stimulation, (6), **Table 2**]. After real stimulation, the mean fatigue reduction was 28% of the baseline (range between 2 and 76%), and 8% after sham (range between −11 and 38%, paired-samples *t*-test real vs. sham, $p = 0.016$).

TABLE 1 | Demographic and clinical profile of people with MS.

	Sex	Age	Dis Dur	EDSS	BDI	mFIS	LrF	9HPT
$S1_{wb}$	9F/4M	45.8 (7.6)	7.6 (8.2)	*1.5* [0–3.5]	12.7 (3.5)	41.6[a] (7.5)[a]	0.38 (0.48)	20.8 (4.9)
$SM1_{hand}$[b]	6F/2M	38.1 (9.8)	13.5 (4.2)	*2* [1–2.5]	11.0 (5.1)	57.1 (19.9)		
	p	*0.080*	*0.068*	*0.254*	*0.438*	*0.062*		

M, male; F, female; Mean or Median in italics and SD, standard deviations () or ranges [min, max] across the group of: Dis Dur, disease duration; Scores of: EDSS, expanded disability status scale; BDI, Beck depression inventory; LrF, lesion relative factor; MFIS, modified fatigue impact scale, and 9HPT, time (s) to execute right hand 9-Hole Peg Test at baseline.

[a]mFIS 1-week apart repetition was 41.5, SD 6.1 (see Study Design). MRI-derived measures (LrF) and 9HPT were not collected in the $SM1_{hand}$ group.

[b]Two out of the 10 patients of the $SM1_{hand}$ group dropped out. In the last row, the significance og the comparison between the two groups.

TABLE 2 | Transcranial direct current stimulation treatment effects on fatigue.

	Real		Sham		
	T0	T1	T0	T1	*p*
$S1_{wb}$	**42.1** (7.9)	**31.0** (12.0)	37.2 (7.0)	34.7 (10.4)	0.014
$SM1_{hand}$	57.8 (19.9)	42.1 (17.2)	55.5 (26.6)	52.1 (22.0)	0.239

Mean and SD of fatigue scale (mFIS) across patients before and after 5-day tDCS treatment, stimulating bilateral either whole body S1 ($S1_{wb}$) or hand section of SM1 ($SM1_{hand}$). p is the significance of the Stimulation × Treatment interaction effect. In bold, values with significant difference between pre- and post-treatment, as estimated by post-hoc comparison whenever the Stimulation × Treatment interaction effect was significant.

tDCS Treatment Effect on Fine Hand Motor Control (9HPT)

In the $S1_{wb}$ group, 9HPT of the right hand correlated with both EDSS and physical items of MFIS (Pearson's $r = 0.736$, $p = 0.015$ and $r = 0.744$, $p = 0.014$, respectively). It should be noted that the correlation between MFIS_phys and 9HPT remains substantially stable after correction for EDSS (partial correlation $r = 0.602$, $p = 0.086$). The lesion load was not associated with any clinical or fatigue-related measure (LrF with EDSS, BDI, total or physical MFIS $p > 0.200$ consistently).

The full model ANOVA evidenced, in addition to the right hand performing better than the left [*Hand* factor $F(1,8) = 5.749$, $p = 0.043$, overall average 20.3 ± 4.6 and 22.6 ± 4.3 s, respectively], that the two hands' performances were differently affected by the intervention [*Hand* (Right, Left) × *tDCS intervention* (Pre, Post) × *Stimulation*(Real, Sham) effect $F(1,8) = 5.697$, $p = 0.044$]. Repeating the reduced models for each hand separately, we observed that the left hand did not change after the 5-day stimulation, while the right hand 9HPT changed in terms of dependence on whether the stimulation was real or sham [*Stimulation* × *tDCS intervention* effect $F(1,8) = 5.680$, $p = 0.044$]. The *post hoc* comparison showed that, after the real stimulation, the time required to execute the 9HPT decreased (two-tails paired *t*-test $p = 0.038$, with average 21.1 ± 4.9 pre and 19.8 ± 3.8 s post values], while it was unchanged by sham stimulation (*t*-test $p = 0.401$). No association emerged among post-tDCS values of MFIS regarding either total or physical and 9HPT scores.

Hand SM1 Stimulation ($SM1_{hand}$)

No interaction *Stimulation* × *Treatment* effect was observed when $SM1_{hand}$ electrode was used ($p > 0.200$, **Table 2**), indicating that effects of real and sham stimulations on fatigue levels were not clearly different.

M1 Excitability

No differences were observed in RMTs, stimulation intensities or MEP latencies when compared between hemispheres, between stimulation types (Real or Sham) or treatments (pre–post-stimulation) ($p > 0.200$ consistently). In the $S1_{wb}$ group, the mean of RMT across all conditions was $58.4 \pm 2.6\%$ of the maximal stimulator output, TMS intensity was $70.2 \pm 3.1\%$, MEP latency

was 27.3 ± 3.2 ms. In the $SM1_{hand}$ group, the RMT decreased after stimulation (paired-samples *t*-test $p = 0.004$; pre 59.2 ± 18.8 and post 55.0 ± 17.9% of the maximal stimulator output), while the latency did not change 24.4 ± 2.6 ms. MEP latency was associated to the MS severity (EDSS–MEP latency Pearson's coefficient $r = 0.880$, $p = 0.021$).

Motor evoked potential amplitude distribution definitely differed from a Gaussian and we obtained a good fit by natural logarithmic transformation (Shapiro–Wilk $p > 0.200$ consistently).

No association was evident between the order of MEP collection and its amplitude (Pearson's correlation $p = 0.607$). Mean MEP amplitude, estimated as exponential back-transformation of mean of logarithm-transformed MEP amplitudes, were 171.5 ± 1.8 for the right OP and 145.3 ± 1.9 for the left OP. No difference of baseline MEP amplitudes was observed between Real and Sham stimulations (*t*-test $p = 0.380$ averaging right and left values).

In the $S1_{wb}$ group, the ANOVA on the MEP amplitude showed a trend interaction effect *Stimulation* × *Treatment* ($p = 0.073$), which corresponded to an increase of MEP amplitude after the real stimulation (*Treatment* effect, $p = 0.037$), absent after Sham ($p = 0.275$). The average increase with respect to the baseline level was 6.0% ranging between 0.2 and 22.6% of baseline level (MEPpost–MEPpre/MEPpre of logarithm-transformed MEP amplitudes averages).

In the $SM1_{hand}$ group, MEP amplitude increased after the real stimulation (*Treatment* effect, $p = 0.021$). The average increase with respect to the baseline level was 40.4% ranging between 16.7 and 76.0% of baseline level.

No association emerged among post-tDCS MEP values and 9HPT scores.

S1 Excitability

No effects were observed in the N20 SEP component between the two hemispheres or the two stimulations (pre–post-stimulation, Real or Sham, $p > 0.200$ consistently). The N20–P25 complex showed a tendency to increasing after the stimulation, but no *Stimulation* × *Treatment* effect was found ($p > 0.200$).

Relationships Between S1 and M1 Excitability and MFIS Variations

Fatigue level changes did not correlate with variations in M1 excitability in either of the $S1_{wb}$ or $SM1_{hand}$ subgroups ($p > 0.200$ in both cases).

Discussion

Our 5-day tDCS stimulation targeting the bihemispheric whole body somatosensory region significantly decreased MS fatigue. In addition, hand muscle MEPs showed that that stimulation modified M1 excitability, whereas MN SEPs showed no evidence of changes in S1 excitability.

Mechanisms Behind Regional Dependence of tDCS Treatment Efficacy (i.e., S1-Whole Body vs. SM1-Hand)

Overall, the 5-day tDCS treatment targeting the bilateral $S1_{wb}$ representation showed the *Stimulation* × *Treatment* effect, which was lacking in the $SM1_{hand}$ intervention. Noteworthy, the average decrease in mFIS score was 15.6 after real $SM1_{hand}$ stimulation – larger than the 11.1 point decrease observed after real $S1_{wb}$ stimulation, with similar baseline levels – and the specific paired *t*-test comparison was significant ($p = 0.030$). We also analyzed why an average net (real minus sham) SM1 effect of 15.6–3.4 = 12.2 was not significant while an average net S1 effect of 11.1–2.4 = 8.7 was significant, with comparable SD (a little bit larger in S1, indeed) (although such a comparison is irrelevant in the absence of a significant interaction). The reason lies in the different correlation patterns: within the $SM1_{hand}$ subgroup, correlations are absent between Sham and Real baseline levels, as well as between fatigue scale values from other time points, contrasting clear (and expected) correlations in the $S1_{wb}$ subgroup (**Table 3**).

TABLE 3 | Intra-cohort fatigue levels correlation.

	$S1_{wb}$		$SM1_{hand}$	
	ρ	*p*	ρ	*p*
Real vs. Sham T0	**0.718**	0.045	−0.299	0.471
Real T0 vs. T1	**0.840**	0.002	0.403	0.323
Sham T0 vs. T1	**0.957**	0.000	−0.054	0.900

Pearson's correlation coefficients (ρ) and significance (p) between real and sham baseline mFIS scores (T0) and between mFIS scores at baseline (T0) and after-treatment (T1) both after real (second row) and sham (third row) treatments, for both the $SM1_{hand}$ and $S1_{wb}$ subgroups. In bold, significant correlations.

The $S1_{wb}$ treatment was more effective than over $SM1_{hand}$ (21) and than over the left prefrontal cortex (30). This comparative result strengthens the working hypothesis, which guided the development of the S1-whole body personalized electrode. In fact, data available in the literature document a failure of the inhibitory mechanisms in the frontal and primary motor (M1) areas involved in motor planning (4), a reduced M1 ICI before and after fatiguing exercises (4), and an increase in M1 excitability (4) in fatigued vs. non-fatigued MS patients and to healthy subjects. Concurrently, together with excessive excitability of M1, we observed signs of a reduced S1 excitability (10). Moreover, we observed an altered parieto-frontal projection, mainly involving S1 and M1, in fatigued vs. non-fatigued MS patients (13, 31). Thus, we decided to neuromodulate to enhance selectively the excitability of S1, avoiding a direct enhancement of M1 excitability (as occurs with SM1 electrode), to further support the parieto-frontal projection already observed by tDCS (12).

Suitability of Differentiated Effects Targeting S1 vs. SM1

Transcranial direct current stimulation-generated modulations of cortical excitability can be focused by means of proper sizing and positioning of the stimulation electrode. Since tDCS efficacy is determined by the current density (i.e., current strength/electrode area), we can obtain increased focality by reducing the electrode size while keeping a constant current strength. In the motor system, Nitsche and colleagues (32) compared tDCS effects on central representations of two muscles, first dorsal interosseus (FDI) and abductor digiti minimi (ADM), by measuring MEPs. Stimulation with small electrodes (3.5 cm^2) generated focal effects, with different MEP amplitude increases for the two muscles (32). The protocol we are proposing actually requires less focality than

Nitsche's, where a discrimination of M1 neuronal pools controlling the two hand muscles was sought. In fact, we intend to stimulate motor vs. sensory regions. However, while positioning of tDCS electrodes in M1 stimulation can be guided by TMS, which induces responses from specific muscles, a neuronavigation system is required when stimulating S1 vs. M1 to precisely identify the central sulcus. Modern frameless stereotaxic systems allow navigation on the subject's structural MRI-derived brain representation, providing high-spatial precision with accuracy in the range of millimeters (33). In our experimental setup, we used precise topographical determination of the central sulcus in placing the $S1_{wb}$ electrode (6, 14, 25, 34).

tDCS Targeting Bilateral vs. Mono-Hemispheric Regions

Multiple sclerosis fatigue is not associated to mono-hemispheric prevalence, as shown by electrophysiological (10) and neuroimaging data (9). Thus, via the tDCS intervention, we targeted bilateral (35) either whole body S1 or hand SM1. In the present results, we observed bilateral M1 enhancement, documenting that bilateral stimulations of a homologous area do not cancel out. This hypothesis of ineffective bilateral M1 stimulation is derived from the well-known motor system organization, with M1 of one hemisphere inhibiting M1 of the other hemisphere. Through bilateral stimulation of homologous M1 areas, the concurrent increase of inhibition induced by the increase in excitability of one hemisphere might thus cancel out the increase in excitability in the other hemisphere. However, we can reject such a hypothesis, and we can also speculate that a relevant component of the presently observed neuromodulation operates directly on local pyramidal neurons, and not via inhibitory or excitatory networks beneath the electrode (36, 37).

Brain Plasticity Induced by S1 Stimulation

We did not find evidence of S1 excitability changes induced by $S1_{wb}$ tDCS treatment, as measured by the typical SEP assessment. This can be due to two causes. The first is that the SEP gives an indirect assessment of cortical pyramidal neurons with respect to TMS-derived MEP. In fact, TMS stimulates pyramidal neurons and the MEP muscle response gives a measure of cortical excitability with as a single-station-pathway (only the spinal cord relay in between). Instead, the pathway between MN stimulation and S1 (here assessed by single-derivation SEP) includes spinal cord, brain stem, and thalamic relays. The second reason can be poor sensitivity of EEG-derived SEP analysis. In addition, we found more effects in M1 than in S1, which can be due to non-selective S1 stimulation. Via simulations (in progress), we are in fact observing that the induced current density is slightly prevalent in S1 but it is of a comparable intensity also in M1.

Study Limitations

We did not study the two datasets ($S1_{wb}$ and $SM1_{hand}$ 5-day tDCS treatments) in a single statistical model, since a different anode electrode size (anode electrode area of 70 cm^2 for SM1 and 35^2 for S1) and a different reference position (on Oz or on the left shoulder) were used.

Here, we investigated somatosensory evoked responses, since we performed a stimulation planned to focus on S1. We started from a standard single derivation in each hemisphere to assess SEP changes. Nevertheless, we collected 64-channel EEG data to further investigate cortical effects. In particular, source analysis will allow future investigations of our main hypothesis of a modification induced by the tDCS treatment on sensory-motor functional connectivity.

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The role of fMRI to assess plasticity of the motor system in MS

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Neuroplasticity in the motor system has been extensively investigated by functional MRI (fMRI) in multiple sclerosis (MS) patients; we report results obtained by both task-related and resting-state fMRI studies. Furthermore, the possibility to manipulate neuroplasticity in MS will also be addressed.

TASK-RELATED fMRI STUDIES

The first works on fMRI and the motor system reported greater cortical activation in patients with relapsing–remitting (RR) or secondary progressive (SP) MS than in healthy subjects (HS) during a simple finger flexo-extension hand movement (1, 2). This increased activity also involved the ipsilateral hemisphere, especially in patients with more severe axonal damage (2). Increased cortical activity during the performance of the same simple motor task was also observed in patients with primary progressive MS (3). In the same years, we described a large increase in motor activation, with a greater involvement of the ipsilateral hemisphere, in MS patients following a first clinical episode of motor deficit from which they had fully recovered (4). In a subsequent study, we assessed cortical activity during the same thumb-to-finger opposition task in patients with a clinically isolated syndrome (CIS) after clinical recovery, divided into an optic neuritis group and a paresis group (5), with the aim to better investigate patterns of motor reorganization. A greater involvement of the ipsilateral hemisphere in the paresis group, not only versus HS but also versus the optic neuritis group, suggested that neuroplastic changes in the motor system contribute to the recovery and maintenance of a normal motor function level, despite the presence of structural damage.

Functional MRI activation during a motor task should be viewed as a dynamic phenomenon that changes during the disease course. In a single-case study, Reddy and collaborators reported a progressive reduction in cortical over-activation paralleling motor improvement after a clinical relapse and NAA recovery at spectroscopy (6). We longitudinally evaluated 18 patients with RRMS by performing two fMRI studies in the remitting phase, on average 20 months apart (7). Decreased ipsilateral motor activation, which inversely correlated with age, progression of T1 lesions and occurrence of new relapses, was observed at follow-up. In other words, in patients with a less severe disease course, motor activation tended to return to a more normal pattern. In keeping with our findings, Mezzapesa et al. reported that pseudotumoral MS lesions affecting the motor system lead to the recruitment of pathways in the ipsilateral hemisphere; good recovery after relapses is associated with function recovery in the contralateral motor areas and decreased ipsilateral activation (8).

New insights come from task-related fMRI studies in different MS phenotypes. In a cross-sectional study, Rocca et al. evaluated patients with CIS, RRMS, or SPMS (9). They found various patterns of motor activation, which spread as the phenotype became clinically more severe: a more lateralized pattern in CIS, a more bilateral pattern in RRMS, and the recruitment of additional areas, even outside the motor system, in SPMS. Therefore, over-activation does not necessarily represent adaptive plasticity since it may even be associated with a high disability, as observed in SPMS; it is conceivable that over-activation, to some extent, limits the clinical manifestations of tissue damage, without fully compensating.

The MS widespread microstructural damage, as shown in combined diffusion tensor imaging (DTI) and fMRI studies, correlates with increased sensorimotor network activation (10, 11). A strict correlation between over-activation of the motor areas and structural damage specifically located along the cortico-spinal tract has been documented, suggesting a compensatory role (4, 12). On the other hand, over-activation in the ipsilateral motor cortex significantly correlated with callosal damage (11, 13), suggesting that increased activity in the ipsilateral motor cortex is likely due to decreased inhibitory input of trans-callosal fibers and thus represents a marker of disease severity rather than a mechanism of adaptive plasticity.

Multiple sclerosis patients display greater cortical activation than HS even during passive movements of a limb, which, unlike active movements, are not affected by individual motor impairment (6, 14). In agreement with the data yielded by active movements (9), passive movements of the hand induced a progressive extension of activation to the ipsilateral hemisphere according to the clinical phenotype (HS < RRMS < SPMS) (15). Deactivation of posterior cortical areas belonging to the default mode network (DMN) increased in RRMS, though not in SPMS, if compared with HS; activation in the contralateral sensorimotor cortex was significantly correlated with deactivation in the DMN in HS and RRMS, though

not in SPMS. These findings suggest that disorganization between anti-correlated functional networks is due to a higher level of disconnection.

RESTING-STATE fMRI STUDIES

Recent years have witnessed a growing interest in the study of resting-state functional connectivity (rs-FC) in MS aimed at understanding alterations in the intrinsic functional architecture of the MS brain and their role in disease progression and clinical impairment. Resting-state fMRI (rs-fMRI) can be used to identify anatomically separate, though functionally connected, brain regions configuring specific RS networks (16, 17); unlike fMRI during movement execution, rs-fMRI is not influenced by task performance, which may differ from that of HS, especially in patients with motor disability.

Some studies have reported a reduced rs-FC in the sensorimotor network in MS. Lowe et al. demonstrated a bilaterally reduced rs-FC in the motor cortices in patients with varying degrees of MS, both in the resting state and during finger tapping, thereby showing that both these fMRI approaches differentiate patients with MS from controls (18). In a large group of RRMS patients with a wide range of disabilities and disease durations, Rocca et al. found decreased rs-FC in regions of the sensorimotor network in RRMS when compared with HS; moreover, the authors hypothesized a link between the reduction in rs-FC and severity of tissue damage (19).

In contrast, other studies have reported increased rs-FC in the motor network in early MS (20) and in RRMS patients with mild disability (21); they suggested that the rs-FC increase is an early phenomenon of cortical reorganization that is lost as the disease progresses. A recent multi-center study revealed a significant generalized increase in rs-FC within the sensorimotor network in a heterogeneous group of MS patients, which once again points to a potential role of this rs-FC widespread enhancement in maintaining brain functionality (22).

Several factors may explain the discrepancies between studies reporting decreased or increased rs-FC in MS, including differences in the patients' clinical characteristics (e.g., in clinical subtype, disease duration, and clinical disability), number of subjects enrolled, and methods used for both image acquisition and analysis. However, when the findings of these studies are considered together, they point to a functional reorganization of the motor network in MS patients, which is present from the earliest disease stages.

More recently, some studies attempted to explore the clinical correlate of motor rs-FC alterations in MS. Indeed, although the ability of rs-fMRI to detect brain functional reorganization in MS has been proved, the role of FC alterations in the pathogenesis of MS, as well as the potential relationship between resting-state network reorganization and clinical disability, remain unclear.

In a recent work, Janssen and collaborators demonstrated reduced intra-network connectivity in the motor network in RRMS patients, associated with higher levels of disease severity, thus pointing to the possibility that resting-state changes may serve as a biomarker of disease progression (23). On the other hand, increased connectivity in the left premotor area was found to be associated with greater clinical disability in RRMS though not in SPMS (24). This finding suggests that even if disease progression is related to disrupted FC within the motor network, increased FC in specific motor areas may represent an attempt to compensate for the functional impairment, at least in RRMS.

MODULATION OF NEUROPLASTICITY

The objectives of neuroimaging studies should be to distinguish between beneficial and non-beneficial (maladaptive) neuroplastic changes and to understand whether, and if so how, we can modulate brain plasticity to enhance cortical activity changes associated with a clinical improvement. Studies on the effects of drugs or motor practice on cortical activity are particularly interesting in this regard (25–29).

In a double-blind, crossover, placebo-controlled study, we evaluated the short-term effect of a single dose of 3,4-dyaminopyridine (DAP), a K-channel blocker shown to improve motor function and fatigue, in RRMS patients with mild disability (26). fMRI during a right-hand movement demonstrated greater activation in the right motor areas after 3,4 DAP compared with placebo, which was instead associated with a subjective improvement in fatigue. Similarly, TMS led to reduced intracortical inhibition and increased intracortical excitation after 3,4 DAP compared with placebo. We therefore concluded that this drug might improve motor function by enhancing excitatory synapses.

The effects of a short motor training in MS patients have been reported in two task-related fMRI studies, though with discrepant results (28, 29). Morgen et al. showed that MS patients did not display any decrease in motor activation in the contralateral primary motor and parietal cortices after motor training, which in HS is interpreted as adaptation to a simple, automated movement. Mancini et al. instead showed that motor training induces a progressive decrease in cerebral activation in sensorimotor system areas in both HS and MS patients, thereby suggesting that the physiological process of short-term adaptation to a simple motor training is preserved in MS.

Tomassini et al. showed that both short- and long-term (15 days) visuo-motor practice induced the same level of improvement in HS and patients (25). Moreover, their fMRI study revealed changes in activated areas, which, however, differed between patients and HS. Their results suggest that neuroplasticity induced by visuo-motor practice is preserved in MS, although underlying mechanisms differ from those in healthy people.

This conclusion is supported by our recent work on FC changes in early RRMS patients (27), who were studied by rs-fMRI before and after a short motor training, i.e., a 25-min repetitive thumb flexion with the right hand, that closely resembled that described in previous fMRI studies (24, 25). The study of the sensorimotor (SMN) and cerebellar (CBN) networks revealed no pre-training rs-FC differences between MS patients and HS; differences did instead become manifest after motor practice. The SMN displayed post-training FC increase in both groups, which, however, reached statistical significance only in HS, whereas the CBN FC significantly increased in RRMS alone. Interestingly, following motor training, a significant correlation was observed in patients between the rs-FC of the SMN and CBN, suggesting an emerging inter-network synchronization. Furthermore, the FC increase in the SMN

significantly correlated with tissue damage, as assessed by lesion volume and fractional anisotropy. The manipulation of the resting-state to define its dynamics might be a valid way to investigate functional connectivity alterations in patients.

CONCLUSION

Functional MRI studies exploring the motor system in MS have demonstrated the ability of the brain to reorganize itself as a response to the disease. Functional reorganization develops in relationship with structural disconnection, making the structural substrate evaluation essential. Despite the undeniable progress in fMRI techniques, clinical interpretation is still controversial and no single technique has proved adequate to predict clinical evolution, ultimately because of the knowledge gap between brain connectivity and function.

Future studies integrating rest and task fMRI (30) might allow us to obtain the "best of both worlds" by shedding light on altered interactions between those two brain function states. Within the context of RS–FC characterization, there is growing interest in the analysis of the intrinsic dynamics of RS time courses and spatial maps (31). This type of assessment (32) has already revealed alterations in DMN dynamics in early MS subjects. Network analysis tools, based on inter-network correlations and graph theoretical analysis, are also very promising (33). Task-manipulated resting-state to elicit altered responses in MS opens perspectives for assessing targeted functions. The nature of changes observed in fMRI will be established in the measure of our further knowledge on brain's dynamics, under task and/or in resting-state; the ambition is to reveal every patient's potential for experience-dependent plasticity, thus pinpointing a target for neurorehabilitation and identifying successful intervention markers.

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Neuroplasticity and motor rehabilitation in multiple sclerosis

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INTRODUCTION

Motor symptoms are common and disabling across the phases and forms of multiple sclerosis (MS). Disease modifying treatments help to prevent their development, but most of their management is through rehabilitation. Current rehabilitation approaches are based on physical therapy tailored to the individual's needs (1). The efficacy of these approaches, however, is limited, as it is purely based on clinical grounds, and is largely unpredictable in the individual case, where several factors, including location, extent, and severity of MS damage, can contribute to individual variation in rehabilitation outcomes (2–7). Therefore, an improved understanding of the neural processes underlying functional recovery and driven by rehabilitation, as well as the development of novel recovery interventions that fully exploit the individual patient's potential to recover motor function remain a clinical necessity and a research priority (8).

NEUROPLASTICITY UNDERPINS RECOVERY OF MOTOR FUNCTION IN MS

Plasticity is the ability of the nervous system to adapt to the ever-changing conditions of the environment, encountered during development and learning (9–11). Within the central nervous system, such plasticity is sustained by a variety of changes in gray matter (e.g., neurogenesis, synaptogenesis, changes in neuronal morphology), in white matter (e.g., changes in the number of axons, axonal diameter, fiber density, axonal branching and trajectories, myelination), and in other tissue compartments (e.g., glial cell size and number, angiogenesis) (12).

Experimental and clinical studies suggest that brain plasticity also occurs in disease (13), where adaptation to damage contributes to the preservation or to the recovery of function (14, 15). In MS, the bulk of evidence suggests that plasticity limits the clinical impact of damage, by establishing patterns of brain activity different from those of healthy volunteers, and accompanies improvements in motor performance with practice, by adaptively reorganizing those altered patterns (6). Indeed, studies on spontaneous recovery after a MS relapse show that changes in activation patterns occur with the resolution of active inflammation (16–18) and parallel recovery of motor function (16, 18). Recovery-oriented interventions can also drive these changes further by reorganizing or restoring altered patterns of brain activity (19) and improving behavior even at higher levels of disability and damage (5). Such interventions may also induce clinically meaningful changes in brain structures (20–23), possibly as a result of activity-dependent remyelination.

Not all of the changes in brain activity occurring in MS are adaptive and thus behaviorally beneficial. Evidence suggests that plasticity can also be maladaptive and thus contribute to or sustain disability (24, 25). Indeed, maladaptation may help to explain the functional differences that are observed between clinical stages and forms of MS (26), beyond individual variation in adaptive plasticity and structural reserve. Evidence of maladaptation calls into question, the increase in MS damage as the only factor that limits functional reorganization, as maladaptation itself can contribute to incomplete recovery and progression (27). Probing the limits of plasticity is challenging in MS because of the widespread and multifaceted nature of the disease, with the involvement of both gray and white matter (28), within (29), and outside (30) MS lesions, in the brain as well as in the spinal cord (31). The combination of neurophysiological methods and network-approach to data analysis can offer ways to probe the brain plastic reserve (6) and its behavioral consequences (32). Future interventional studies that interfere with cortical function or studies that assess concurrent structural changes may also disambiguate the relative contributions of inefficient versus insufficient versus ineffectual plasticity (6).

THE EXPLOITATION OF NEUROPLASTICITY PROMOTES AND ENHANCES REHABILITATION-DRIVEN MOTOR RECOVERY

To promote the individual's potential for recovery in MS by exploiting adaptive plasticity, we need to test novel recovery interventions that combine a strong biological rationale with monitoring of clinically meaningful functional and structural brain reorganization. For these studies, the methodology and neuroscientific rationale need to be carefully considered.

Methodologically, optimized trials that use enriched designs to manipulate behavior through interventions would offer a novel experimental framework for testing efficiently the promotion of adaptive plasticity. Markers of recovery that combine clinical and neurophysiological measures

could provide insight into the clinically meaningful mechanisms of plasticity and offer a tool for early detection of effects of intervention. Markers predictive of recovery could improve stratification of patients in clinical trials, while developing a personalized approach to recovery-oriented interventions. Technology, especially in the field of neuroimaging [e.g., high field magnetic resonance imaging (MRI)], novel measurements, and sophisticated network-level analysis (33, 34) can now meet this increasing demand for novel markers and predictors. The development of computer-based behavioral measurements also offers sensitive and objective ways to target even subtle deficits and quantify behavioral improvements (35).

Neuroscientifically, an improved knowledge of changes in the brain that accompany functional recovery remains crucial, with the need to distinguish truly adaptive versus maladaptive changes (24), and changes representing compensation versus those representing restitution (36). Additionally, the development of novel strategies for motor recovery requires an improved understanding of the properties of the normal motor system, such as its flexibility and the stability of induced functional and anatomical changes, which vary with development (37) and previous experiences (38, 39) and thus inevitably influence the plastic response to damage (13). Approaches that adopt pharmacological and/or non-pharmacological modulation of neuroplasticity to enhance functional recovery represent promising strategies (6). While they pose methodological challenges in terms of prediction of response, qualification of markers of recovery, and development of appropriate outcome measures, these approaches hold promise for clinically meaningful benefits (6) and open therapeutic opportunities for more disabled cohorts (40, 41). Combining experimental evidence with clinical studies will offer a scientifically grounded rationale to develop novel interventions that may predispose (42), promote (5, 19), or enhance (6) plasticity underlying functional recovery. In this regard, future therapeutic approaches with novel disease modifying treatments hold promise for combined preventative and neuroprotective (43) or restorative (44) effects that increase further the prospects of and scope for functional recovery.

CONCLUSION

Rehabilitation of motor function is a major component of MS management that is supported by neuroplasticity, i.e., the brain's ability to adapt to MS damage or disability. Developing novel and more effective rehabilitation approaches, therefore, requires an improved understanding of brain plasticity that can be exploited in recovery interventions. The need for novel rehabilitation approaches, underpinned by promoted and enhanced neuroplasticity, challenges traditional experimental designs. This challenge can be addressed using methodological advances, especially in neuroimaging, which allow improved understanding of mechanisms and detection of intervention effects. In this article, we provide a critical overview of the current knowledge of neuroplasticity and its modulation in MS motor rehabilitation and we offer a vision for future directions of research in this field.

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Functional plasticity of the visual system in multiple sclerosis

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Multiple sclerosis (MS) can affect the visual system at all anatomical sites from the retinal nerve fiber layer (RNFL) to the visual cortex. MS demyelinating lesions most commonly occur at the level of the optic nerve, causing acute episodes of optic neuritis (ON) (1). ON usually determines a moderate to severe visual impairment, followed by a complete or near complete clinical recovery within a few weeks. However, even after visual recovery, a permanent structural and functional damage of the anterior visual system can be detected by visual evoked potentials (VEP), MRI, and RNFL imaging (2). Two hypotheses, which do not exclude each other, are commonly advocated to explain such clinical–paraclinical paradox. The first suggests that axons of the optic nerve can maintain a normal clinical function up to a critical threshold of nerve fibers loss, as a result of the intrinsic structural reserve (also known as neuroaxonal redundancy) (3). The second supports the role of adaptive functional changes taking place at the level of striate and extra-striate visual cortical areas (4–8).

While the first hypothesis is extremely difficult to test *in vivo* – even applying advanced structural MRI techniques such as diffusion tensor imaging (DTI) – the second hypothesis has been repeatedly tested by functional MRI (fMRI) during visual stimuli or, more recently, resting conditions.

Adaptive neuroplasticity is formally defined as the reorganization of distributed patterns of brain activity that accompany action, perception, and cognition, and that compensate for impaired function resulting from disease or brain injury (9). On the other hand, non-adaptive neuroplasticity refers to functional cortical reorganization not associated with any benefit on brain function.

Using visual-stimulated fMRI, MS patients in the early stages of ON have consistently shown a reduced response to visual stimuli in the primary visual (striate) cortex when compared to healthy controls (HCs) (4–6). These investigations support the hypothesis that during the acute phase of ON, the function of the primary visual cortex is significantly affected by a substantial reduction of the afferent inputs due to damage to the optic nerve. Other fMRI studies on ON have widened the view has led to wider in depth knowledge reporting significant functional changes occurring at the level of peristriate and extra-striate visual cortices as well (6–8, 10). Recruitment of extra-striate areas, in particular, has been shown at the level of the insula, claustrum, thalami, lateral geniculate nuclei, corpus striatum, orbitofrontal and lateral temporal cortices, posterior parietal cortex, and lateral occipital complexes (LOCs) (7, 9, 10). Among the abovementioned areas – for many of which the exact effect (i.e., adaptive or non-adaptive) on visual recovery still needs to be clarified – LOCs, higher order visual areas located within the ventral processing stream and involved in identification and recognition of objects, have consistently showed relevant functional changes associated with ON (7, 8). In a preliminary study conducted during the earliest stages of ON, patients with a better visual acuity at baseline showed a stronger activation of the LOCs, independently of VEP latencies and severity of optic nerve damage (7). The potential adaptive role of LOCs on visual recovery after ON was further supported by a longitudinal study, showing that over-activation of LOCs at baseline was associated with a better visual outcome at 1 year, independently of anterior visual pathway structural damage. Such findings were strengthened by the negative prognostic value of reduced LOCs fMRI responses at baseline (8).

Although visual-stimulated fMRI studies have allowed to comprehend relevant aspects of functional changes occurring in visual cortical areas during ON, they are intrinsically limited by the fact that the measured signal changes mostly reflect the degree of anterior visual pathway damage rather than intrinsic activity of visual cortical areas. Moreover, since optic nerve damage is highly variable between subjects with ON, there is a wide inter-subject variability, which further undermines the results and interpretation of visual-stimulated fMRI studies.

Given these premises, resting-state (RS) fMRI has a relevant role as it overcomes most of the abovementioned limitations, and allows to explore spontaneous (self-generated) activity of cortical visual areas.

In the study by Roosendaal et al., – the first to explore the visual RS network (V-RSN) together with other major RSNs – the authors did not find any significant changes in both clinical isolated syndrome (CIS) and relapsing remitting (RR) MS patients when compared to each other and HCs. Such findings were not surprising since the study was not designed to explore the relationship between V-RSN

changes and ON. Indeed, no historical data on previous ON, no clinical/instrumental evaluation of the visual function, and no measures of optic nerve damage were acquired (11).

Using a similar approach, Faivre et al. explored all main RSNs, including the V-RSN, to compare early RRMS patients with HCs. Similarly to the Roosendaal study, data acquisition and analysis did not take into account previous episodes of ON. Nevertheless, the authors were able to demonstrate functional rearrangements inside multiple regions of the V-RSN (i.e., lingual gyrus, left middle occipital gyrus, and left cuneus), thus showing significant neuroplastic changes of this RSN in MS patients (12).

In order to specifically explore the effect of previous ON on intrinsic V-RSN connectivity, we investigated a population of 30 RRMS patients [16 without (nON-MS) and 14 with (ON-MS) previous ON] and 15 HCs (13). For this purpose, all subjects underwent a 3TMRI including RS-fMRI data acquisition, a neurological examination, and a thorough ophthalmologic evaluation, based on the assessment of visual acuity as well as the measurement of RNFL thickness. When the entire group of RRMS patients was compared to HCs, a weakened V-RSN connectivity was found in RRMS patients at the level of inferior peristriate cortices (along the fusiform gyri), bilaterally. The subsequent comparison of ON-MS versus nON-MS patients showed a spot of stronger functional connectivity (FC) in the right extra-striate cortex (along the middle occipital gyrus; MOG) as well as a spot of reduced FC in the right inferior peristriate cortex, in ON-MS patients. Notably, all detected V-RSN changes did not co-localize with regional gray matter atrophy.

Since our patients with RRMS showed a significant damage of the anterior visual pathways and until now there have been no other RS studies conducted on ON, we compared our results with those obtained in non-MS diseases affecting the anterior visual pathways, such as Leber hereditary optic neuropathy and early blindness (14, 15). In agreement with our findings, these studies reported significant functional changes at the level of the V-RSN (14, 15).

Our data, therefore, confirm and complement previous photic-stimulated fMRI studies, showing that visual recovery after ON might be associated with cortical reorganization within extra-striate visual areas (6, 7, 10). In particular, one might speculate that an enhanced RS FC at the level of the right MOG might either reflect a sustained and protracted recruitment or a loss of inhibition of this area after ON.

Although the study of the V-RSN has certainly added relevant information on ON-related neuroplastic changes taking place at the level of the striate and extra-striate cortex, the current lack of longitudinal studies do not allow to discriminate between adaptive ad non-adaptive changes.

CONCLUSION

To date, visual plasticity of the visual system in MS has been investigated especially after ON.

Relevant cortical functional changes have been consistently described at the level of striate and extra-striate areas using either photic-stimulated or RS-fMRI studies.

Available evidences also suggest that some of the observed neuroplastic changes, in particular, those occurring at the level of the occipital extra-striate cortex (e.g., LOCs and MOG), might act as adaptive neuroplasticity, thus impacting positively on visual recovery after ON.

Once the functional plasticity of the visual system related to ON in MS will be further elucidated it might become a useful model to evaluate the effect of new neuroprotective or (adaptive) plasticity-promoting molecules.

PERSPECTIVES

Future investigations will have to further assess adaptive and non-adaptive neuroplasticity of the visual system in MS patients. More specifically, cross-sectional and longitudinal studies will have to address, which cortical functional changes are associated to functional recovery after ON. Once the methodology will be set up and standardized in a multicenter context will be able to assess the effect of old or new MS drugs on mechanisms of visual recovery after ON.

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Network collapse and cognitive impairment in multiple sclerosis

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FUNCTIONAL REORGANIZATION IN MS: AN OUTDATED CONCEPT?

The current field of multiple sclerosis (MS) research is an active and highly interesting one: structural abnormalities such as inflammatory lesions and brain atrophy are studied with a wide array of advanced neuroimaging techniques (1). These techniques are subsequently used to try to explain the large clinical heterogeneity in patients. Clinically important in MS is cognitive dysfunction, which is present in 40–70% of all patients (2, 3). Cognitive impairment in MS receives much attention, as there is currently no proven effective treatment, but symptoms may nevertheless start in early stages of disease already (4). Cognitive decline is known to exert deleterious effects on psychosocial functioning (2, 5, 6). Traditional structural imaging measures like lesion volumes are notoriously poorly related with cognitive function (7), so a move toward more sensitive, comprehensive measures is required, such as those that measure brain function in addition to brain structure.

Historically, most early imaging studies have used the paced auditory serial addition test (PASAT) to study cognition in MS, a task that measures information processing speed (8–10). These observed a combination of hyperactivation of frontal regions in response to the task and a recruitment of additional areas, not normally attributed to the task in controls. The functional changes were mostly positively related to the amount of structural damage in the brain, and were stronger in patients who scored normally on the PASAT, indicating that it might be a beneficial process. Later studies investigated other cognitive domains and also showed such an apparently beneficial increased local activation, for example, during a memory task in the hippocampus (11) and during the N-back working memory task in the dorsolateral prefrontal cortex (DLPFC) (12). Importantly, these studies also showed decreased activation in cognitively impaired patients.

The body of literature of that point in time led to our previous hypothesis of functional reorganization in MS (13). This hypothesis asserted that a "compensatory" change is seen in the brains of MS patients in the form of an increase in brain function, i.e., both increased activation and increased connectivity. Functional connectivity is conceptually quite different from task-based activation and reflects the amount of communication between brain regions, i.e., coherent patterns of firing typically measured with correlation measures. Early connectivity studies investigated the so-called "default mode network" (DMN), which is only coherently active during a resting state. Two such studies found DMN changes that were interpreted in the same way as the task-based activation studies: increased DMN connectivity in clinically isolated syndrome (CIS) patients (14) and decreased DMN connectivity in progressive MS, which was related to cognitive impairment (15). We proposed that increasing structural damage, in combination with an optimum curve of "functional reorganization," results in a delayed, non-linear, development of cognitive dysfunction.

However, the previous model was mostly based on task-based activation studies, while the connectivity field was still in its infancy. As the concept of functional reorganization was gaining support, the field was primed for finding cognitively relevant connectivity changes. Interestingly, recent studies have mostly related increased functional connectivity to cognitive dysfunction, raising doubts on the previous concept of functional reorganization in MS. In this paper, we will review this recent functional connectivity literature and reiterate the case around functional connectivity changes in MS and their potential effects on cognition. Which reported connectivity changes can be justifiably said to be "compensatory" or "beneficial"? Which are likely "maladaptive"? Can any such predicate be arrived at all, based on the neuroscientific studies available? Is it perhaps time to revise our previous model of functional reorganization?

FUNCTIONAL CONNECTIVITY IN MS: A FIELD OF CONTRADICTIONS

Resting state network changes have been observed in relapsing remitting MS (RRMS) patients, both within and between almost all resting state sub-networks (16). The DMN de-activates when performing a task, and appears to be strongly related to cognition. DMN changes have been difficult to place within our previous hypothesis, as cognitive dysfunction was related to both decreased (17–21) and increased DMN connectivity (22–24). In pediatric MS, increased DMN connectivity was seen in cognitively preserved patients in the anterior cingulate gyrus, while decreased connectivity of the posterior cingulate was seen in cognitively impaired patients (25). Increased connectivity of the anterior cingulate cortex was also found in adult

MS patients, although these connectivity changes showed both positive and negative correlations with cognitive dysfunction (26). Another recent paper in adult-onset MS suggests that the severity of cognitive impairment is directly related to the level of increased functional connectivity of the DMN (27). As the DMN deactivates during tasks, task-based studies have also looked at this network. During performance of the N-back working memory task, researchers noted less deactivation of the DMN (12) in cognitively impaired patients. Another recent study, however, seems to contradict this finding, as an increased DMN activation during a similar task was related to both higher intellectual enrichment and information processing speed performance (28). In short, the DMN results have been difficult to interpret.

Unfortunately, results from seed-based analyses investigating other structures like the DLPFC have not been very consistent either. One such study (29) found a reduced connectivity between the DLPFC and the superior medial frontal gyrus in patients who scored normally on the N-back, in relation to increased difficulty of the task, and also found increased connectivity between the left and right prefrontal cortices. This connectivity between the DLPFC and medial frontal regions was increased in MS patients in another study, during the Go/No Go task, at which they were impaired (30). The DLPFC was also studied during performance of the PASAT in patients with CIS who were impaired on this test (31, 32), showing decreased connectivity with several areas, including the anterior cingulate and thalamus. Contrarily, another study only showed increased connectivity during the PASAT in CIS patients, who were also impaired on this test (33).

Studies looking at several other cognitively relevant structures such as the thalamus, hippocampus, and cerebellum have shown varying patterns of connectivity in MS as well. Thalamic atrophy has well-known and strong effects on cognition in MS (34), which appears related to global cortical network changes (24, 35). An aforementioned task-based CIS study showed decreased connectivity between the thalamus and DLPFC during the PASAT (31), at which patients were impaired. Strikingly, during a resting state, the thalamus has also been shown to have increased connectivity with frontal areas in clinically definite MS patients with cognitive impairment (36, 37). Similarly, at rest, the hippocampus showed decreased connectivity related to hippocampal atrophy in patients with still intact memory performance (38), but increased connectivity in patients with memory impairment (39). The cerebellum, however, showed decreased connectivity in patients with cognitive dysfunction, both during the PASAT (40) and Stroop tasks (41).

WHAT DOES IT ALL MEAN?

As described above, the body of literature on cognitively relevant connectivity changes in MS is currently difficult to interpret. As it seems, our previous model for functional reorganization is incomplete and the term is currently used in a number of ways and lacks a clear definition. Additionally, these findings were studied across the spectrum of clinical and cognitive phenotypes in MS, with very different methodological and statistical approaches, leaving the data ambiguous in places. Some studies now refer to any connectivity change as functional reorganization, leaving it to the reader to disentangle "beneficial" or "maladaptive" functional reorganization *post hoc*. This process actually seems quite complicated, however, as cross-sectional studies have related both connectivity increases and decreases to cognitive dysfunction in MS. Therefore, the studies that do claim that changes might be beneficial for cognitive performance in MS might not have enough evidence to do so. In truth, we are currently unable to disentangle "good" from "bad" and are strongly limited by the cross-sectional nature of almost all of these studies.

For example, suppose that a functional connectivity increase is observed in cognitively preserved patients, and a decrease in a cognitively impaired patient group. Although many studies interpret such a finding as cognitively relevant, as described previously, such data could, in fact, be interpreted in several ways. First, the functional connectivity increase in cognitively preserved patients might reflect "beneficial" functional reorganization, delaying cognitive impairment. In impaired patients, this effect of functional reorganization is then lost. Second, the functional connectivity increase in cognitively preserved patients might be a "maladaptive" response, following, e.g., disinhibition, heralding an imminent network collapse, and further deterioration into cognitive impairment. Third, the functional connectivity increase in cognitively preserved patients could be an unrelated epiphenomenon. Or, that the connectivity increase is related to structural damage, but that it has no direct impact on cognition at all. And finally, given the fact that most studies are cross-sectional, it cannot be excluded that the frequently observed functional connectivity increases in patients with cognitive impairment are, in fact, "beneficial." It is possible that such increases are, e.g., a bleed through of beneficial functional reorganization from the cognitively preserved stage. This could be due to a poor definition of cognitive impairment and/or plastic changes that persist throughout this stage of the disease. The only way we are going to understand the cognitive role of functional connectivity changes in MS will be to study them over time.

Preliminary longitudinal studies linking connectivity changes to cognitive rehabilitation (42, 43), as well as pharmacological intervention (44), show some promise. Unfortunately, determining sufficient sample sizes and time frames remains difficult given the current lack of data, leaving these small studies difficult to interpret. Such intervention studies aiming to increase neurotransmitter levels in MS appear logical, as there is an apparent cholinergic (45) as well as glutamate (46) imbalance in MS, which might leave the network unstable. Therefore, pharmacological therapies targeting such neurotransmitters might prove valuable (47). It must be stressed, however, that there may also be downsides to such an approach, as specific glutamate receptor subtypes have been linked to brain atrophy (48) and excitotoxic effects due to the treatment and the functional reorganization process might actually increase tissue damage and network stress.

THE FUTURE: MEASURING NETWORK COLLAPSE IN MS

As the field of functional imaging in MS matured, the clinical interpretation of the *combined set* of functional changes in MS

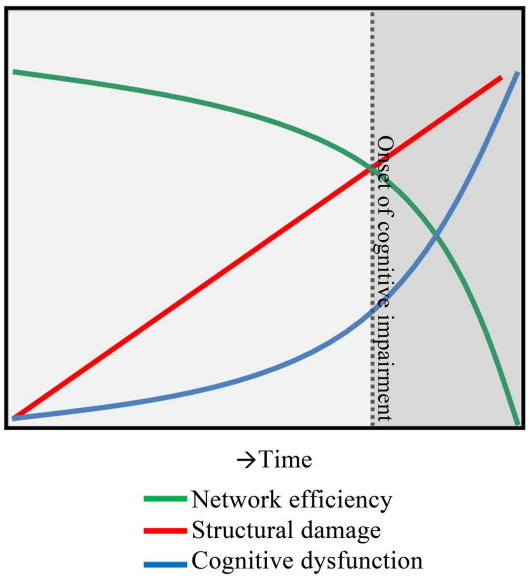

FIGURE 1 | A hypothesis of network collapse as a cause for developing cognitive impairment in MS. In early stages of MS, structural damage is low, leaving network efficiency relatively high. As the structural damage accumulates over time, network efficiency levels drop, inducing a network collapse after a critical threshold (indicated by the dotted line) is exceeded. After this, the network is unable to function normally and cognitive impairment develops.

has become much more complex, leaving our previous model of functional reorganization in MS incomplete and too simplistic. After exploring abovementioned individual structures and subnetworks in MS has not made matters much clearer, it is now opportune to look at connectivity in another way. One option is to take functional connectivity values and convert them into a more holistic network model of the entire brain. This so-called graph analysis approach (49) uses different parameters such as the clustering coefficient and path length (50) to describe network information flow. Applications of these techniques in MS have been very limited (49), but have highlighted the power of graph analysis in discriminating patients from controls (51). Graph analytical studies in MS have shown that cognitive dysfunction is related to an inefficient network, as seen by the change in clustering coefficient and path length (52–54), impaired network integration of information (55) and clustering (56), decreases in network centrality (57, 58), increases in modularity (59), and changes in minimum spanning tree parameters (35, 60). These graph measures provide us many new ways to conceptualize and understand what actually happens to the global status of the entire brain network in patients with cognitive impairment in MS, beyond the poorly understood local increases or decreases in connectivity. Future longitudinal studies are now required to assess the predictive power of these measures. Together, it appears that the brain network of patients with cognitive impairment in MS features a strong decrease in whole-network *efficiency*, i.e., a network "collapse" (see **Figure 1**).

In summary, thinking about functional reorganization processes and labeling them as either "beneficial" or "maladaptive" has proven to be overly simplistic. A more holistic approach is required, encompassing both activation and connectivity data into a frame of network dynamics in a longitudinal fashion. Following this, first steps toward using more sophisticated (functional) imaging tools to monitor cognitive deficits can hopefully be taken.

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All authors contributed to the conception, drafting, revising, and finalizing of the manuscript and agree to be accountable for all aspects of the work.

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Case-based fMRI analysis after cognitive rehabilitation in MS: a novel approach

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Background: Cognitive decline in multiple sclerosis (MS) negatively impacts patients' everyday functioning and quality of life. Since symptomatic pharmacological treatment is not yet available alternative treatment strategies such as cognitive rehabilitation are of particular interest.

Objectives: To analyse the ways in which MS patients respond to cognitive training, by combining behavioral and fMRI data in a case-based triangulation approach.

Methods: Ten relapsing-remitting (RR) MS patients aged between 39 and 58 years and between 1 and 8 years post MS diagnosis were included. EDSS ranged from 1 to 3.5. Participants had normal to high intelligence levels. Six patients were assigned to the training group (TG) and four to the control group (CG) without intervention. The TG received a 4-week computerized working memory (WM) training, consisting of 16 training sessions of 45 min duration each. Before and after the training a neuropsychological examination and fMRI investigation by using an *N*-back task of different complexity was applied.

Results: Patients in the TG responded differently to cognitive training. Four participants did not meet the triangulation criteria for being treatment responders. The two responders showed two distinct changes regarding activation patterns after training: (I) *decreased* brain activation associated with increased processing speed and (II) *increased* brain activation associated with higher processing speed and WM performance.

Conclusion: The occurrence of different and opposed response patterns after the same training indicates a risk in applying classical group statistics. Different and especially opposed patterns within the same sample may distort results of classical statistical comparisons. Thus, underlying processes may not be discovered and lead to misinterpretation of results.

Keywords: working memory, cognitive training, rehabilitation, plasticity, multiple sclerosis, fMRI

INTRODUCTION

For decades, it has been known that patients with multiple sclerosis (MS) suffer from cognitive deficits. However, their importance for both the patients' daily life and the overall health economy has been neglected for a long time. Meanwhile, they are regarded as a major element of the disease. Since symptomatic pharmacotherapy is not available, non-pharmacological approaches might further improve patients' situation. In this context, cognitive rehabilitation has been studied with respect to its effectiveness. Several heterogeneous rehabilitation studies have been conducted, targeting either specific cognitive functions such as attention (1–4) or memory (5, 6) or applying a non-specific neuropsychological treatment. Primarily due to methodological heterogeneities, meta-analyses report negative results (7) or found only low evidence (8) for the effectiveness of cognitive rehabilitation approaches. Rosti-Otajarvi and Hämäläinen (9) report low but nevertheless positive evidence for cognitive training effects on working memory (WM) and other memory functions. However, clear evidence is missing, so far.

Studies using fMRI to monitor the effectiveness of cognitive treatment assume that behavioral improvement after cognitive training may be based on "adaptive" processes in the brain. Most studies report increased and more widespread activation in patients with MS after cognitive rehabilitation (1, 3, 10, 11). While patients receiving cognitive training show overall increased activation, untreated patients often show a decrease over time (12). However, a small trial, including only four participants with MS receiving cognitive training, reported increased activation in posterior regions but decreased activation in frontal areas of the brain (13) highlighting that brain adaptation is not only reflected by increased but also by decreased activation of task relevant areas.

In MS patients, aspects such as disease course, disease activity, cognitive status, fatigue, and depression can impact the responsiveness to cognitive interventions. This heterogeneity may result

in different patterns of response to the same cognitive treatment. In trials with large samples, these influencing factors can statistically be controlled for, however, most rehabilitation studies only refer to small sample sizes. To address this problem, we propose a case-based approach to assess different patterns of response to cognitive training in heterogeneous and small samples. To underline the necessity of studying single patients more carefully, we present a case-series including six patients with early relapsing-remitting MS (RRMS) who received specific WM training during 4 weeks, and four control participants without intervention. The primary aim was to clarify whether (A) MS patients may show different brain activation responses to cognitive training and (B) how these changes in brain activation are finally related to individual cognitive performance. To answer these questions, a triangulation approach was applied.

MATERIALS AND METHODS

PARTICIPANTS

Sixteen patients with CIS and early RRMS under interferon-beta-1b (Betaferon) therapy were recruited. Inclusion criteria were as follows: time since diagnosis <10 years, EDSS below 6.0, no relapses 3 months prior to the baseline visit. Participants were randomly assigned to the treatment group (TG; $N = 9$), or the control group (CG; $N = 7$), respectively. In the TG, two patients were excluded because they did not match the inclusion criteria and one was excluded because of an acute relapse during the intervention. From the CG, one patient quit the study because of personal reasons and two more participants were excluded because of relapses during the study.

The remaining 10 participants (TG = 6; CG = 4) were aged between 39 and 58 years and were between 1 and 8 years post MS diagnosis. Time since last relapse was shorter in the TG (0.25–4.4 years) than in the CG (2.7–6.4 years). EDSS ranged from 1 to 3.5. T2 lesion volume was between 0.24 and 8.53 ml. Participants had normal or high intelligence level. Baseline characteristics of participants are displayed in **Table 1**. The participants gave written informed consent to participate in the study, which was approved by the local Ethics Committee (Basel).

STUDY DESIGN

All participants underwent two baseline neuropsychological assessments within 2 weeks to assure a stable cognitive baseline status. During the second assessment, a baseline brain imaging (structural MRI and fMRI) was performed. All participants in the TG started their computerized cognitive training (BrainStim) within 1 week after the second baseline testing. They trained for 4 weeks, four times a week, for 45 min. Participants trained at home and were supervised once a week by a trained psychologist. Computerized training sessions were logged to monitor adherence to training. Participants in the CG received no intervention. Within 1 week after completion of the training, participants were retested for cognitive performance and a second MRI/fMRI was conducted.

To analyse the case series, a triangulation approach was applied as it is used in qualitative research (14). This methodological procedure combines quantitative and qualitative aspects (15). In order to measure a response to the treatment, detectable changes in more than one outcome parameter are taken into account. By applying this method to our case-series, response to treatment was defined by a combined change in brain activation on the one hand and cognitive functions (WM and/or processing speed) on the other. To overcome the problem of different scaling and to allow for direct comparisons between fMRI and cognitive outcomes, we intentionally avoided pre-defined cut-off values but focused on a qualitative description of changes by visual inspection.

THE COGNITIVE TRAINING TOOL BrainStim

BrainStim (16) is a computerized training tool based on the WM model of Baddeley (17). It consists of three different modules targeting both, verbal and visual–spatial aspects of WM (18, 19). The first module trains spatial orientation. Participants have to memorize either a visually or verbally described route. This route has to be retraced on a virtual map afterwards. The number of crossings increases with higher levels of difficulty. A second module trains visual memory as well as the updating function of the central executive component. Participants have to remember the location of cards that have been turned over and back again. The task is to find

Table 1 | Baseline characteristics and possible factors for treatment response.

Case	Gender	Age	Disease duration (years)	Number of relapses	Last relapse prior to study	EDSS	T2 lesion volume (ml)	General intelligence	Depressive symptoms	Cognitive fatigue	Motor fatigue
TGI	Male	47	2	6	9 months	3.5	0.27	96 PR	No	Severe	Severe
TG2	Female	44	1	2	3 months	1.0	5.93	50 PR	No	No	Moderate
TG3	Female	42	2	4	7 months	3.5	0.31	50 PR	No	Moderate	Severe
TG4	Male	42	5	2	4 years 5 months	2.0	0.24	99 PR	Mild	Moderate	Severe
TG5	Female	52	3	2	8 months	2.5	8.53	93 PR	No	Mild	Severe
TG6	Female	58	2	2	6 months	2.0	2.05	93 PR	No	Mild	Moderate
CGI	Male	46	8	4	6 years 5 months	1.0	1.43	99 PR	No	No	No
CG2	Female	42	3	3	3 years 2 months	2.5	1.38	73 PR	Moderate	Severe	Severe
CG3	Male	39	3	1	2 years 8 months	1.0	2.67	96 PR	No	No	No
CG4	Male	52	2	1	3 years 6 months	2.0	4.61	79 PR	No	Severe	Severe

PR, percentile rank.

pairs of cards with corresponding figures. With increasing levels of difficulty, the number of cards in one set is increases. During the third module, participants have to remember digits, presented in a limited period of time, and recall them after having performed an arithmetic distraction task. With each increase of the level of difficulty, more digits have to be recalled.

BrainStim is designed to ensure training not only based on repetition and practice but also on the development and consolidation of strategies. Therefore, the stimuli of the modules are presented randomly, where the order of the modules is changing in each session. The level of difficulty adapts automatically to the participants performance. After a pre-defined number of correct responses, the level of difficulty increases. Whenever the participant fails to solve a certain amount of tasks, the level of difficulty is decreases again.

COGNITIVE ASSESSMENT

At the first baseline visit, we collected demographical data and assessed premorbid intelligence [MWT (20)], fatigue [fatigue scale for motor and cognitive functions: FSMC (21)], and depressive symptoms [BDI-fast screen (22)]. Based on previous work (18) where BrainStim has proven its specific effect on WM and processing speed, we defined these functions as primary cognitive outcome measures. The *Corsi Block backwards* task was used for visual WM and the *Digit Span backwards* test for verbal WM [Wechsler memory scale-revised (23)]. The *symbol digit modalities* test (SDMT) was used to measure WM performance and processing speed (24). To receive a measure for processing speed that is not confounded with WM, we used the *alertness* tasks (tonic and phasic) from of the *test battery for attention performance* [TAP (25)]. Age corrected normative data was available for all cognitive tests. For WM (Corsi Block bw and Digit Span bw) as well as for alertness (tonic and phasic) percentile ranks <16 were regarded as a clinically meaningful cognitive deficit. SDMT scores were z-transformed according to Scherer et al. (26) and z-scores less than -1.68 were rated as clinically significant.

fMRI PARADIGM

During fMRI, participants solved a N-back task with different WM loads [adapted from the TAP (25)]. Series of pseudo-randomized digits were continuously presented on a screen. Participants were asked to press a button as fast as possible whenever the target appeared. A target was a digit that was identical to the immediately preceding digit (1-back), the second to the last digit (2-back), or the third to the last digit (3-back). A block design was used for semi-randomized presentation of the N-back conditions and rest condition (fixation cross). One active block with a duration of 30 s consisted of 10 stimuli with 2 stimuli being targets. Each condition was presented four times during each session. Participants performed the paradigm two times with a break between the two sessions. In sum, each condition was presented during eight blocks. Reaction times for N-back tasks were logged, but due to technical problems this files were not available for all participants and time points and therefore excluded from further analysis. Immediately prior to the MRI, participants were familiarized with the N-back task outside the scanner to ensure comprehension.

MRI DATA ACQUISITION

The MR measurements were performed on a 3.0-T scanner (Magnetom VERIO, Siemens Healthcare, Erlangen, Germany) with a standard head coil. An anatomical image for registration purposes was acquired [sagittal T1-weighted 3D high resolution magnetization-prepared rapid gradient echo (MPRAGE) sequence: TR/TE/TI = 2000/3.37/1000 ms, 256 × 256 matrix, field of view (FoV) = 256 mm, providing an isotropic spatial resolution of 1 mm^3]. For lesion masking, a T2-weighted fluid attenuated inversion recovery (T2-FLAIR) sequence was obtained (TR/TE/TI = 8000/77/2370 ms, 40 slices with slice thickness of 3 mm and FoV = 220 mm).

Echo-planar imaging (EPI) sequences were used for functional imaging (TR/TE = 2000/23 ms, 34 slices with a slice thickness of 3 mm, FoV = 256 mm, voxel size = 4 mm × 4 mm × 3 mm). Slices were positioned parallel the AC–PC line. For both runs with the paradigm, 262 volumes with a total scan time of 8.5 min were recorded. After excluding the 5 five dummy scans per run, 514 volumes remained for further analysis.

MRI DATA MANAGEMENT AND ANALYSIS

Data were analysed using Statistical Parametric Mapping software package, SPM8 (http://www.fil.ion.ucl.ac.uk/spm). We identified T2 hyperintense white matter lesions with the lesion segmentation toolbox [LST (27)]. To choose the optimal initial threshold κ, lesion segmentation was run with different thresholds. Afterwards, two independent evaluators compared manually the resulting lesion maps with the original raw images. By this approach, an initial threshold of $\kappa = 0.2$ was chosen. Lesion masks were used for automatic lesion filling with intensities similar to the normal white matter voxels in T1-weighted images. We used these "lesion-free" T1-images for later registration steps. Further, the lesion-filled T1-images were segmented into gray matter, white matter, and CSF ("new segment"). Gray matter and white matter were fed to DARTEL to create a study-specific template (28).

fMRI data were realigned, unwarped, and co-registered with the T1-images. fMRI images were then normalized to MNI space with the corresponding DARTEL flow fields and a 8 mm Gaussian smoothing.

Since we were interested in changes between the two time points, all smoothed images were subject to a first-level analysis to define the model design and contrasts of interest. Movement parameters extracted from the realignment step were included as additional covariates in order to remove residual variance. Contrasts for changes between baseline MRI and the post-training MRI in each subject [$p < 0.001$, threshold: 10 voxels per cluster (29)] for all performance conditions (1-back, 2-back, and 3-back) were specified to identify activation increase and decrease between the times of measurement.

RESULTS

fMRI ASSESSMENT

For fMRI outcomes, contrasts between baseline and post-training for 1-back, 2-back, and 3-back conditions for each participant were built individually. Patterns of response were comparable for the three conditions. Therefore, only contrasts from the 2-back condition are displayed in **Figure 1** for clarity reasons ($p < 0.001$

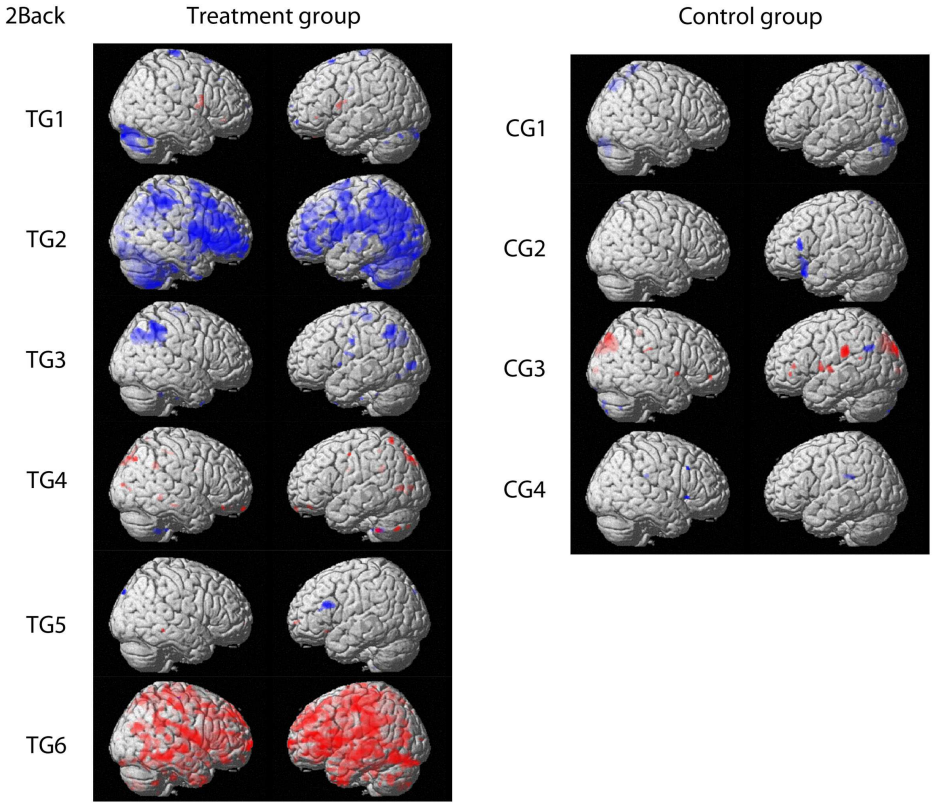

FIGURE 1 | Contrasts comparing baseline and post-training fMRI results for the treatment group and the control group, respectively. Activation increase is marked in red whereas decreased activation over time is highlighted in blue ($p < 0.001$ uncorrected; threshold: 10 voxels per cluster). Figures are shown in radiological convention.

uncorrected, threshold: 10 voxels per cluster). Four participants (TG1, TG3, TG4, TG5) receiving the training showed only minor changes in brain activation, which were comparable to changes observed in participants without training.

Two participants (TG2, TG6) showed changes in brain activation that exceeded changes observed in patients without training. One participant (TG2) showed decreased activation in primarily frontal and parietal regions. In TG6, the opposite pattern was observed. This participant showed increased brain activation spread across the whole brain except for the occipital lobe.

NEUROPSYCHOLOGICAL ASSESSMENT

At baseline, no participants were impaired regarding tonic alertness and SDMT. Three participants (TG2, TG5, CG2) had reduced phasic alertness of whom one participant (CG2) showed reduced visual WM span (corsi block backward) in addition. One participant (TG1) showed reduced verbal WM performance (digit span backward). On a group level, by applying Mann–Whitney-*U* test performance on the digit span backward in the CG was higher than in the TG whereas no other baseline differences were detectable. (Note: Although this work is focused on qualitative single subject analyses the authors included this information revealed by group analyses on explicit request by one reviewer.)

For longitudinal comparisons, we used raw scores as displayed in **Table 2**. When comparing baseline and post-training results, none of the participants showed a consistent increase in all cognitive domains. One TG participant (TG3) showed solely an increase in the visual WM task. Participant TG1 performed faster during both alertness tasks. Two participants (TG2, TG4) showed faster reaction times in the alertness tasks and increased scores in the SDMT. TG5 had increased WM functions but no speed increase. TG6 performed better after the training in four of the five outcome measures. In the CG, two participants (CG1, CG3) showed increased verbal WM scores, one participant (CG2) had faster reaction times during the alertness task and higher visual WM scores. CG4 showed faster reaction times during the phasic alertness task. Three participants of the CG (CG1, CG3, CG4) had decreased reaction times during tonic alertness after 4 weeks. No participant of the CG showed changes in the SDMT task. On group level, there were no differences between the TG and the CG after the training. (Note: Although this work is focused on qualitative single subject analyses the authors included this information revealed by group analyses on explicit request by one reviewer.)

DISCUSSION

To identify possible effects of WM training on brain functionality and cognitive status, we presented six cases with RRMS

Table 2 | Raw scores of primary cognitive outcome measures for all participants at baseline and after the training.

	Processing speed measures				Processing speed and WM (SDMT)		WM measures			
	Tonic alertness (TAP alertness A)		Phasic alertness (TAP alertness B)				Visual WM (corsi blocks bw)		Verbal WM (digit span bw)	
Case	**Baseline**	**Post-training**	**Baseline**	**Post-training**	**Baseline**	**Post-training**	**Baseline**	**Post-training**	**Baseline**	**Post-training**
TG1	266.5	242.0	251.5	217.0	50.5	54.0	9.5	10.0	5.0[a]	5.0
TG2	285.5	260.0	280.5[a]	264.0	65.0	75.0	9.0	9.0	6.0	5.0
TG3	293.0	293.0	247.5	248.0	56.5	59.0	7.5	9.0	6.0	7.0
TG4	242.0	227.0	233.5	204.0	45.5	61.0	10.0	10.0	7.0	8.0
TG5	276.5	271.0	312.0[a]	307.0	57.5	66.0	8.5	10.0	5.0	8.0
TG6	255.0	246.0	258.0	242.0	63.0	72.0	8.5	10.0	5.0	6.0
CG1	214.0	223.0	220.5	223.0	56.5	55.0	9.0	10.0	9.5	11.0
CG2	272.0	243.0	301.5[a]	235.0	56.5	59.0	7.0[a]	9.0	7.0	7.0
CG3	235.5	249.0	228.0	232.0	65.5	67.0	10.0	11.0	8.0	11.0
CG4	235.0	268.0	259.5	243.0	47.5	43.0	7.0	8.0	6.0	5.0

Improvements from baseline to post-training are highlighted in gray.

Alertness (TAP) scores represent reaction times.

bw, backward; WM, working memory; TG, training group; CG, control group.

[a] *Clinically meaningful baseline values (PR < 16 for alertness and WM tasks; z < −1.68 for the SDMT).*

receiving WM training during 4 weeks and four control cases without intervention. At a purely descriptive level, the key differentiators between TG and CG were SDMT and tonic alertness. Four out of six cases in the TG were able to increase their performance on the SDMT, whereas no participant in the control condition did so. Regarding tonic alertness, four of six participants in the TG showed higher performance after the training whereas three out of four participants in the CG showed even a performance decrease.

Regarding functional brain activation, four TG participants showed only minor changes in brain activation, which were comparable to changes observed in the CT. We therefore conclude that these minimal changes reflect a normal range of variation during a 4 weeks period and not a response to training.

Two TG participants met our triangulation criteria for being responders: both changes in brain activation and changes in WM or processing speed measures were observed. One participant showed a *decrease* in activation during the training period in frontal and parietal regions. The other responder showed an *increase* in brain activation in frontal and parietal regions as well as an additional increase in temporal regions.

The opposed response to treatment measured by fMRI might be reducible to different brain processes. Plasticity processes related to practice have been studied intensively in healthy individuals. Group analyses regarding short-term WM training (duration of training: 30–120 min in total) in healthy adults revealed decreased brain activation in frontal (dorsolateral, prefrontal, inferior frontal, precentral sulcus) and parietal regions (30–33), whereas more intense training led to mixed patterns of increases and decreases (34–37). In their review article, Kelly et al. (38) described four different patterns of change in brain activation due to practice: decrease, increase, redistribution, and reorganization. In a subsequent meta-analysis, Buschkuehl et al. (39) described the same patterns of response to WM training:

(1) Decrease in extent or strength of activation within one network that is associated with higher performance has often been reported after short-term training, mainly based on practice (30, 32). It is thought to be associated with a certain sharpening of response within the network where less neurons are firing in response to a task. This change might reflect more efficient information processing in the brain. The decrease of brain activation within the WM network in one of our responders might be related to this process. This change in activation was accompanied by an increase in processing speed on the behavioral level (Alertness and SDMT; for summary see **Table 3**). Thus, this increased processing speed can be regarded as the behavioral expression of more efficient information processing within the brain.
(2) A second pattern is referred to increased activation within one network (40). Here, increased intensity of activation is thought to be associated with a strengthening in response to a specific task, whereas increase in extent of the activated network reflects additional recruitment of cortical units. None of our participants showed a comparable change in brain activation.
(3) Combined increase and decrease within a network might occur in response to cognitive training (34, 41). This is referred to as redistribution of activation. The same cognitive process is used to solve the task, but due to practice and learning less attention control is needed and task specific processes are

Table 3 | Summary table of changes from baseline to post-treatment for all participants.

Case	Change in activation	Processing speed measures		Processing speed and WM (SDMT)	WM measures	
		Tonic alertness (TAP alertness A)	Phasic alertness (TAP alertness B)		Visual WM (corsi blocks bw)	Verbal WM (digit span bw)
TG1		↑	↑			
TG2	↓	↑	↑	↑		
TG3					↑	
TG4		↑	↑	↑		
TG5				↑	↑	↑
TG6	↑	↑	↑	↑	↑	
CG1		↓				↑
CG2		↑	↑		↑	
CG3		↓				↑
CG4		↓	↑			

empty spaces, no change; ↑, increase; ↓, decrease; bw, backward; TG, training group; CG, control group; WM, working memory.

more involved. None of our participants showed a similar pattern of change in brain activation.

(4) The fourth pattern of response can primarily be seen in clinical populations (38). In contrast to redistribution processes, where involved anatomical structures remain the same, reorganization processes include decreased activation in some areas and additional recruitment of new cortical regions. This shift of activation is thought to reflect a process shift: due to training, other cognitive processes become involved in solving the task. Additional recruitment of temporal regions outside the usual WM network in our second responder might reflect such a reorganization process. At the behavioral level, this participant showed higher processing speed (Alertness and SDMT) and visual WM performance potentially resulting from a reorganization process. The increase of activation was more apparent in the left hemisphere. We assume that the individual has developed a verbal coping strategy, which triggered the observed change in activation after training.

It should be noted, that non-responding participants and participants of the CG also showed changes regarding cognitive performance. Changes in the CG might reflect normal variations in performance, since improvement was isolated on single tests and never consistent across all tests within a single cognitive domain. Changes in non-responding participants of the TG in contrast were more systematic. One of these participants showed increased processing speed (Alertness and SDMT), whereas another participant performed better in all WM measures (SDMT and visual and verbal WM). However, these behavioral changes were not accompanied by changes in brain activation and thus triangulation criteria were not fulfilled.

We are aware that this case-series has several limitations. A first limitation is certainly the small sample size. Second, we did not predefine cut-off values for behavioral and fMRI changes. Third, observed changes in brain activation and cognitive performance might be the result of factors not assessed in the study. To exclude at least variations resulting from the circadian cycle, cognitive and fMRI assessment were always performed at the same daytime. Fourth, changes in fMRI might be caused by variability in the method itself (42). That is why these well-known intersession differences were partly controlled by the applied triangulation approach. Fifth, we used a passive CT instead of implementing a shamed training group (TG). Therefore, it cannot be excluded that changes in the two participants in the TG result from multiple factors such as motivation, social interaction, and emotional support. Sixth, only few participants showed significant cognitive deficits when compared to normative data. Thus, higher baseline performance might reduce the potential to observe significant changes induced by cognitive training due to a simple ceiling effect. A last limitation of the present study is that performance data from the *n*-back task during fMRI was missing due to technical problems. Therefore, fMRI activation patterns could not be compared directly to WM and speed performance inside the scanner but only to the performance outside the scanner in terms of a transfer effect.

These limitations might have modified the outcome of our case-series. Still, we were able to identify two different types of changes after cognitive training in patients with early RRMS: (A) a decreased brain activation, which was associated with increased processing speed and (B) a reorganization process, associated with higher processing speed and WM. The occurrence of different or even opposed patterns of response after the same training indicates a problem with traditionally applied group statistics. Different and especially opposed patterns within the same sample will distort results of classical statistical comparisons. Underlying processes may therefore remain concealed.

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OPINION
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Cognitive reserve as a useful concept for early intervention research in multiple sclerosis

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Cognitive Impairment in Multiple Sclerosis

Multiple sclerosis (MS) is a lifelong progressive neurologic disease typically diagnosed between ages 20 and 40 years: a time when persons are striving to accomplish normative goals of young adulthood (e.g., establishing a career). More than half of MS patients suffer cognitive decline [for review, see Ref. (1)] especially memory problems and cognitive inefficiency (e.g., slowed processing speed, difficulty multi-tasking).

Clinico-Pathologic Dissociation

There is great variability in cognitive status across MS patients, even among patients with similar patterns of disease burden/progression (2, 3). This is evidenced in part by the relatively modest/incomplete correlation between MS disease burden (e.g., T2 lesion volume, cerebral atrophy) and cognitive functions, whether studied cross-sectionally [e.g., Ref. (2)] or longitudinally [e.g., Ref. (3)]. That is, some MS patients are better able to cope with disease burden without cognitive deficits. [Note: there is an important and advancing literature on the relationship between cognition and MRI parameters in persons with MS [e.g., Ref. (4–6)], although a thorough review of this literature is beyond the scope of this opinion piece. In each case, however, the relationship between disease burden and cognitive outcomes remains incomplete.] This dissociation between disease burden and cognitive outcome is common in other neurologic diseases as well, including Alzheimer's disease (AD) (7–9). Indeed, some persons accumulate substantial AD neuropathology (e.g., beta-amyloid) without dementia, whereas other persons suffer dementia at comparable or even lower levels of pathology (8, 9). These observations have motivated the question: how are some people better able to withstand neurologic disease burden without cognitive impairment?

Importance of Prediction and Early Intervention to Prevent Cognitive Decline

Systematic reviews report little-to-no efficacy of pharmacological (10) and behavioral (11) treatments for memory impairment in MS patients. As such, the best treatment of cognitive impairment in MS may be the proactive prevention of cognitive decline in the first place. Similarly, treatments for memory impairment in persons with AD have proven largely ineffective, and research has recently shifted toward very early pre-clinical intervention to prevent the onset of dementia (which may represent a point of no return). The science and clinical practice of early intervention/preventative medicine hinges on our ability to accurately identify patients at greatest risk for future cognitive decline or dementia. Targeted enrollment of at-risk patients into early intervention trials will improve statistical power, because beneficial effects of early treatment can only be observed if the

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non-treatment group declines. Enrolling at-risk patients ensures that there will be adequate cognitive decline for the early intervention to moderate. Clinically, at-risk patients could be targeted for early interventions to help prevent future cognitive decline, and earlier treatment takes advantage of the brain's capacity for plastic reorganization, which is ostensibly greater at younger ages. Finally, if risk and protective factors are modifiable, then knowledge of such factors can inform treatment decisions and/or counseling of patients regarding healthy life choices. First, however, we need to advance our ability to accurately identify MS patients at greatest risk for future cognitive decline.

Cognitive Reserve Against Cognitive Decline

The disconnect between disease burden and cognitive status (i.e., differential cognitive decline) is explained in part by the cognitive reserve hypothesis (12–14), which posits that enriching life experiences protect against cognitive decline in the face of aging and neurologic disease, likely due to greater capacity and efficiency of neural networks (15, 16). Support for the cognitive reserve hypothesis has come from evidence that older adults with a history of greater educational or occupational attainment (17, 18) or engagement in cognitively stimulating leisure activities (19–21) are at reduced risk for dementia. Importantly, the later work showed that cognitive leisure activity (e.g., reading, hobbies) among healthy elders reduced risk for incident dementia in the future, suggesting that consideration of such behaviors in elders may be a useful predictor of future cognitive decline. Note also that engagement in intellectually enriching activities moderates/attenuates the deleterious effect of AD neuropathology on cognitive status in elders (22, 23). Taken together, there is now amble observational evidence within the aging literature that lifetime intellectual enrichment and current cognitive leisure activity lower risk for dementia.

Work by myself and others has extended the cognitive reserve hypothesis to MS [for review, see Ref. (14)], showing that MS patients with greater education (24–27) and literacy/vocabulary (estimated with vocabulary) (28–31) are protected against disease-related cognitive inefficiency and memory problems. We have also shown, however, that cognitive leisure activity (e.g., reading, hobbies) contributes to cognitive status in MS patients independently of lifetime enrichment (estimated with vocabulary) (32), and that engagement in such leisure activities during early adulthood moderates/attenuates the negative effect of disease burden (T2 lesion volume) on current cognitive status in MS patients (33). Others have also shown a benefit of leisure activity against cognitive impairment in MS (34–36). Longitudinal research on reserve against cognitive decline has been more limited; however, Benedict and colleagues have shown that greater intellectual enrichment protects against decline in cognitive efficiency over nearly 5 years (24), and we have shown that enrichment is protective against decline in cognitive efficiency and memory over 4.5 years (31). Longitudinal research highlights the potential clinical importance of considering a patient's level of lifetime enrichment (easily assessed with vocabulary knowledge), which may be a useful predictor of future cognitive decline (thereby helping to identify at-risk patients).

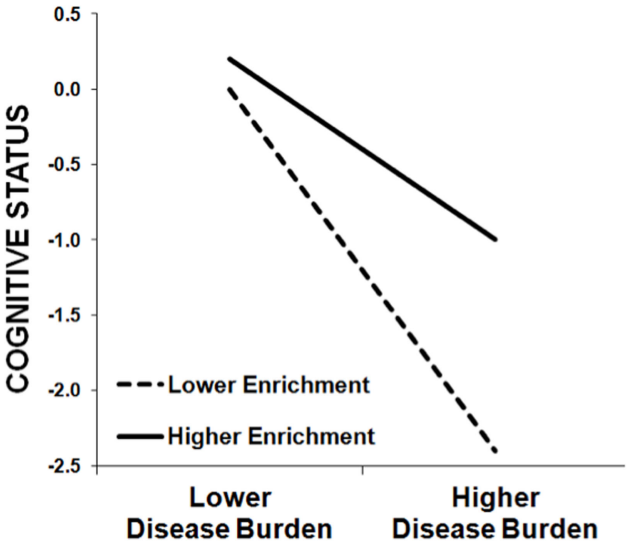

FIGURE 1 | This schematic demonstrates the protective effect of enrichment against cognitive impairment in MS patients, whereby the negative relationship between cognitive status (*y*-axis) and MS disease burden (*x*-axis) is stronger among patients with lower enrichment (dashed line) relative to patients with higher enrichment (solid line). That is, higher enrichment attenuates the negative effect of MS disease burden on cognitive status. (Note that this schematic was not derived from actual data, but instead represents the typical pattern of results we have observed previously.)

On the one hand, we are not surprised that education predicts cognitive outcomes, as such correlations are observed in healthy persons as well. Importantly, however, the theory of cognitive reserve is not based on this main effect of enrichment; rather, cognitive reserve is instantiated in a moderation/interaction. Higher enrichment moderates/attenuates the negative relationship between a disease-related variable (e.g., lesion volume, cerebral atrophy) and a cognitive outcome (e.g., memory). As such, the negative impact of disease burden on cognition is actually greater in persons with lower enrichment than persons with higher enrichment (see **Figure 1**). In fact, we have previously demonstrated that the amount of variance in cognitive outcomes accounted for by disease burden (e.g., cerebral atrophy) actually varies based on the educational attainment of the MS sample, with a stronger relationship between disease burden and cognitive outcomes in samples with lower education (28). The theory of cognitive reserve posits that greater intellectual enrichment protects persons with MS from the negative impact of disease burden on cognition, leading to different trajectories of cognitive decline over time [e.g., Ref. (31)].

Brain Reserve Against Cognitive Decline

Separate from the cognitive reserve hypothesis, the theory of brain reserve capacity (37) proposes that cognitive impairment emerges when brain volume falls below a critical albeit unspecified threshold. This theory has been supported by observations that elders with larger head circumference or intracranial volume [proxies of the brain's maximal lifetime brain growth (MLBG)] are at reduced risk for cognitive decline or dementia (38, 39). MLBG

is considered a proxy of neuronal/synaptic count [see Ref. (40)], and greater neuronal/synaptic count may (a) be linked to more robust neural networks resistant to disease-related disruption and/or (b) provide more potential degrees of freedom for the brain to plastically reorganize in the face of aging or disease-related challenges. We have recently shown that larger MLBG lowers risk for cognitive impairment in MS. Specifically, larger MLBG (estimated with intracranial volume) moderated/attenuated (a) the deleterious link between MS disease burden (e.g., T2 lesion volume) and cognitive efficiency in a cross-sectional sample (33), and (b) decline in cognitive efficiency over 4.5 years in a longitudinal sample (31). Note that MLBG was unrelated to memory function within our MS samples, and closer inspection of the aging/AD literature suggests that MLBG is protective against cognitive inefficiency rather than episodic memory deficits [for discussion, see Ref.(33)]. Note that our cross-sectional (33) and longitudinal (31) research showed that intellectual enrichment protects against cognitive inefficiency independently of MLBG, which is important given the robust moderate correlation between brain size and intelligence (41).

Clinical consideration of MLBG may help identify patients at greatest risk for future cognitive impairment, and such patients can be targeted for early intervention rehabilitation. Note that MLBG is almost completely heritable (42) and therefore outside of one's current control; however, patients could be counseled regarding brain healthy choices (e.g., exercise, diet), which may prevent/slow the loss of reserve brain volume. For instance, cigarette smoking is particularly damaging for MS patients, and should be strongly discouraged (43). Also, psychological stress can exacerbate MS (44), and stress management training has reduced inflammatory MS lesions (45). Finally, adherence to pharmaceutical treatments is linked to preservation of function (46), as disease-modifying therapies are effective in reducing cerebral atrophy (preserving brain reserve) in MS patients (47). This notion of maintaining brain reserve by avoiding risk factors for neuropathology is reviewed elsewhere as the concept of "brain maintenance" in aging (48).

Building Reserve Against Cognitive Impairment

Cognitive reserve is an appealing concept. It suggests that persons can reduce their risk of age- or disease-related cognitive decline by actively pursuing intellectually enriching lifestyles. Note, however, that evidence for the cognitive reserve hypothesis in aging and neurologic populations is almost entirely observational, thereby preventing causal statements about the protective effects of cognitive stimulation. As such, a great deal of more rigorous work is needed before we can "prescribe" specific programs of enrichment, including true experiments/randomized controlled trials of intellectual enrichment. That said, engagement in mentally stimulating activities represents a cost-effective, non-invasive way for healthy persons and MS patients to actively participate in their own cognitive health. This is non-trivial, as the unpredictable nature of MS disease often results in an external locus of control (49), leading to hopelessness and depression. MS patients should be encouraged to remain cognitively active from the time of diagnosis onward.

One important avenue for future research will be to identify modifiable neuroanatomical bases for the protective effect of reserve. We have recently linked engagement in cognitive leisure activity to larger hippocampal volume in persons with MS (35), which is consistent with the well-established effects of enrichment on the hippocampus in basic research [for review, see Ref. (50)], as well as links between enrichment and hippocampal volume in older humans (51, 52). Once we identify the neuroanatomical basis for reserve, we can use these as structural targets in early intervention work to evaluate whether preventative treatments have increased reserve. The alternative is to wait for years to see if an early intervention led to differential cognitive decline in the future, but neuroanatomical targets provide more immediate feedback on the efficacy of early interventions. Discovery of modifiable neuroanatomical bases of reserve also allows us to expand our efforts beyond cognitively based interventions (e.g., intellectual enrichment) to include other interventions/protective factors linked to the health of neuroanatomical targets. For instance, regarding the hippocampus, one of the most promising treatments across neurologic populations may be aerobic exercise training. Indeed, basic research reports strong support for the role of exercise in stimulating hippocampal neurogenesis and memory [e.g., Ref. (53)], which is being translated into humans [e.g., Ref. (54), for review, see Ref. (55)]. We have previously reported a case study linking aerobic exercise training to increased hippocampal volume, improved memory, and enhanced default network functional connectivity in MS (56), and aerobic exercise training in progressive MS patients appears promising (57). Outside of aerobic exercise training, there are many benefits of physical exercise for cognition generally in MS patients [for review, see Ref. (58)].

Conclusion

The theory of reserve provides a useful framework for the science and clinical practice of early intervention against cognitive decline in MS patients (i.e., preventative medicine). First, consideration of a patient's MLBG and level of lifetime intellectual enrichment may help identify patients at greatest risk for future cognitive decline. These at-risk patients can be targeted for early intervention cognitive rehabilitation, or research on such treatments. Toward this end, future research should develop and test algorithms to predict risk of cognitive decline in MS patients, which should take proxies of reserve (as well as other risk factors, e.g., smoking) into consideration. Second, intellectual enrichment programs may provide an early intervention treatment in itself; however, all existing evidence is observational, so rigorous experimental work is necessary to establish causal relationships between enrichment and protection against cognitive decline. Finally, the use of MRI or fMRI to identify neuroanatomical or functional markers of reserve will be helpful in providing measurable proxies for increased reserve as outcomes of early intervention trials. Such targets will provide an immediate evaluation of an interventions efficacy to increase reserve, which can then be validated by differential cognitive decline in the future. There is indeed much more work to be done to translate the concept of reserve into a clinically useful tool for prediction of decline, evaluation of treatment efficacy, and treatment itself for MS patients.

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Cognitive rehabilitation in multiple sclerosis: the role of plasticity

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Cognitive deficits are common in multiple sclerosis (MS), documented at many stages of the disease. Both structural and functional neuroimaging have demonstrated a relationship with cognitive abilities in MS. Significant neuroplasticity of cognitive functions in individuals with MS is evident. Homologous region adaptation, local activation expansion, and extra-region recruitment all occur in an effort to maintain cognitive functioning. While much of this neuroplasticity is adaptive, it may also be maladaptive, particularly in individuals that are demonstrating significant cognitive impairment and/or with disease progression. This maladaptive neuroplasticity may come at the cost of other cognitive functions. Studies of cognitive rehabilitation efficacy have also recently applied neuroimaging techniques to establish outcome. Researchers have successfully applied various neuroimaging techniques to study the effects of cognitive rehabilitation in MS including task-based fMRI and resting state functional connectivity across multiple realms of cognition including episodic memory, executive functioning, attention, and processing speed. These studies have demonstrated neuroplasticity in the brains of persons with MS through the documentation of changes at the level of the cerebral substrate from before to after non-invasive, non-pharmacological, behavioral treatment for deficits in cognition. Future research should seek to identify adaptive versus maladaptive neuroplasticity associated with specific cognitive rehabilitation programs within all MS phenotypes to foster the validation of the most effective cognitive rehabilitation interventions for persons with MS.

Keywords: multiple sclerosis, cognitive rehabilitation, neuroimaging, fMRI, cognitive remediation, cognition

COGNITIVE REHABILITATION IN MULTIPLE SCLEROSIS: THE ROLE OF PLASTICITY

Multiple sclerosis (MS) is a progressive neurological disease marked by the development of lesions, or plaques, throughout the brain and spinal cord. The disease has been shown to impact both the white and gray matter of the brain often resulting in permanent disability (1–3). A broad array of symptoms is common in persons with MS, including motor, psychiatric, and cognitive symptomatology (4).

Cognitive deficits are common in MS, with prevalence rates ranging from 43 to 70% (5–7). MS impacts multiple aspects of cognition and may appear either early or late in the disease process. Deficits in information processing speed represent the most common cognitive deficit in MS (8–13). Other prevalent areas of deficit include attention (13, 14), executive functioning (15–17), working memory (18, 19), and long-term memory (4, 20–23). Overall intellectual functioning generally remains intact (24), as do "simple" attention (i.e., repeating numbers) and basic verbal skills (i.e., word naming, comprehension)(25). The clinical presentation is thus typically one of cognitive deficits, sometimes mild to moderate in nature, impacting specific cognitive domains. Due to the fact that the cognitive profile in MS is generally not one of a generalized dementia, cognitive rehabilitation is particularly appropriate for persons with MS. Cognitive deficits can often be specifically identified through a comprehensive neuropsychological assessment and subsequent cognitive rehabilitation can target discrete areas of dysfunction in an effort to improve overall cognitive abilities and quality of life (QoL).

Cognitive dysfunction has been shown to exert a significant negative impact on the every day lives of persons with MS. Persons with MS with cognitive impairment participate in fewer social and vocational activities (25), have higher rates of unemployment or under employment (5, 25–28) and show greater difficulties in doing routine household tasks (25, 29). Deficits in new learning and memory in particular have been shown to result in a reduced ability to make decisions that could affect functioning in everyday life (30) and negatively impact daily living (31–33). Common resultant functional impairments include difficulty with household chores, shopping, completing home repairs, driving, and using public transportation (34, 35). Reduced QoL is often reported (36).

Given the significant impact of cognitive deficits on the everyday lives and overall QoL of persons with MS, it is imperative that we develop and validate mechanisms for effectively treating cognitive dysfunction in this population. Numerous studies have demonstrated cognitive rehabilitation to be effective across many domains of functioning in other neurological populations. For instance, recent systematic reviews have shown that cognitive

interventions can significantly improve functioning in persons with TBI and stroke (37–39). Cognitive rehabilitation has also led to significant gains in the aging population across both objective neuropsychological performance (40) and the performance of daily life activities (41–43), with effects maintained up to 10 years post-treatment (44). There have, however, been considerably fewer studies on cognitive rehabilitation in MS, with many of these studies suffering from significant methodological difficulties (45–48). More recent, well-designed studies have been more promising and have provided evidence of improved objective cognitive performance as well as improvements in everyday life activities following cognitive rehabilitation [e.g., (45, 49–51)].

COGNITIVE REHABILITATION IN MS: THE ROLE OF NEUROIMAGING

The term *neuroplasticity* refers to "the ability of the nervous system to respond to intrinsic and extrinsic stimuli by reorganizing its structure, function, and connections" [(52); p. 1591]. That is, the brain is able to reorganize its structural and functional connections in an effort to maximize functional capacity and "adjust" its resources to cope with cognitive impairments. Changes in functional activation in persons with MS have often been correlated with improved cognitive performance, such as following cognitive rehabilitation; authors have thus interpreted such neuroplasticity as having a positive or "adaptive" outcome (50, 53). However, it is important to recognize that such plasticity may also be "maladaptive." The term "maladaptive plasticity" may be used to refer to cerebral inefficiency in situations in which such neuroplasticity is correlated with cognitive impairment or decline (54, 55).

Neuroplasticity has recently been observed in numerous studies to explain treatment efficacy of cognitive rehabilitation. That is, both structural and functional neuroimaging have been shown to be related to improvements in cognitive abilities in MS following treatment. In studies of cognition in MS utilizing neuroimaging, cognitive impairments in MS have been related to various measures of cerebral integrity including, T2 lesion load (56), cerebral atrophy (57), third ventricular width (58), corpus callosum size (59), and cortical lesions (60). In addition, the wide application of functional neuroimaging techniques to the MS population has demonstrated alterations in patterns of cerebral activation and functional connectivity. Task-based fMRI is a widely used approach to understanding the cerebral resources involved in completing a specific cognitive task. This approach affords researchers the opportunity to examine levels of activation during task performance in specific brain regions. These altered patterns of cerebral activation have been documented during tasks involving attention (61–63), working memory (54, 63–66), episodic memory (64, 65, 67), and processing speed (68). That is, fMRI studies have noted changes in the functional organization of the brain in MS patients compared with healthy individuals. In addition, studies have even noted that patients in early stages of MS activate additional regions during task performance, prior to cognitive deficits being detectable on neuropsychological assessment [e.g., Ref. (69, 70)]. It has been proposed that this additional activation serves as a compensatory mechanism allowing the individual to maintain intact cognitive functioning for a period of time (69, 71, 72). In more severely impaired patients, however, the data are less consistent. Some groups have noted activation patterns to be comparable with controls (62), despite impairments in cognitive performance, with fewer areas of increased activation than is evident in patients in the earlier stages of the disease. This pattern of findings has been interpreted as an inability to access the additional cognitive resources needed to effectively perform the task (73). Others studies have noted increased activation on task-based fMRI in cognitively impaired patients with MS (54, 55), with this increase in activation correlated with worse performance on cognitive tasks. Due to its correlation with *greater* cognitive impairment, this increased activation is deemed *maladaptive* in nature and has been interpreted as neural inefficiency.

Resting state functional connectivity (rs-FC) studies have similarly noted increased activation to be interpreted as either adaptive or maladaptive in nature, depending on the progression of the disease. In contrast to task-based fMRI, rs-FC allows the examination of the communication between different brain regions within neural networks, while at "rest." Increased connectivity during rs-FC is thought to serve as a compensatory mechanism for cognitive deficits early in the MS disease process (71, 74–76). For example, early alterations in neuronal synchronization in rs-FC networks in clinically isolated syndrome (CIS) have been interpreted to be compensatory, indicating cortical reorganization. Such alterations may not be observed with increased brain damage, thought to indicate that such reorganization is finite and only evident early in the disease process (73). Interestingly, other work has noted that when increased rs-FC is found later in the disease process, this increase rs-FC appears to be maladaptive, similar to that which was found in some task-based fMRI studies [e.g., (54, 55)]. That is, increased rs-FC has been shown to be related to increased cognitive dysfunction in MS samples (77). Thus, early in the disease increased rs-FC appears to be adaptive, but later in the disease, these extra connections are associated with worse performance.

Functional neuroimaging techniques thus provide a means of understanding functional reorganization and neural plasticity in response to the disease process. Functional neuroimaging could similarly be used to observe neural plasticity following effective cognitive rehabilitation. The advantage of using functional neuroimaging in conjunction with traditional neuropsychological outcomes is that researchers can observe, not only the traditional behavioral improvements on cognitive tasks but also changes in the functional cerebral architecture underlying such cognitive improvements. Thus, several recent studies have utilized neuroimaging techniques to evaluate the neurofunctional and neuroanatomical changes associated with cognitive rehabilitation in MS samples. These studies have demonstrated neuroplasticity of the brain of the person with MS through the documentation of changes at the level of the cerebral substrate from before to after *non-invasive*, *non-pharmacological*, *behavioral* treatment for deficits in cognition.

Researchers have successfully applied various neuroimaging techniques to study the effects of cognitive rehabilitation in MS including task-based fMRI [e.g., (78)] and rs-FC [e.g., (79)] across multiple realms of cognition including episodic memory (78), executive functioning, attention, and processing speed (45, 50, 51). Studies have even begun to examine longer-term maintenance of such functional changes, documenting sustained plasticity over time (80).

Research conducted utilizing these neuroimaging techniques have consistently demonstrated significantly increased cerebral activity following cognitive rehabilitation [e.g., (50, 53, 78, 79, 81–83)], with numerous researchers noting induced neural plasticity in response to cognitive rehabilitation. As expected, the specific brain regions in which changes in activation patterns are documented post-treatment varies with the treatment protocol investigated, the specific cognitive function targeted for treatment, as well as the imaging protocol applied. Studies also show differences in the documentation of a relationship between these changes in patterns of cerebral activation and changes in behavior documented via neuropsychological assessment. Specifically, some studies have found that the changes on fMRI to correlate with improvement on neuropsychological assessment in the targeted domain [e.g., (50, 53)], while others have failed to document such a relationship [e.g., (84)].

The majority of studies applying fMRI and rs-FC to the investigation of the efficacy of cognitive rehabilitation in MS have focused on the amelioration of attentional deficits. The attention/information processing modules of the cognitive therapy program, the RehaCom (85), have been far received the most attention. Filippi et al. (50) utilized both fMRI and rs-fMRI to examine the cerebral impact of cognitive retraining in 10 persons with MS that completed treatment and 10 that did not complete treatment. The treatment protocol examined consisted of a portion of the RehaCom addressing attention, information processing, and executive functioning. An improvement in cognitive functioning was noted on the Wisconsin card sorting test (WCST; a test of executive functioning), the paced auditory serial addition test (PASAT; a processing speed and working memory test), and controlled oral word association from pre to post-treatment. While no differences were noted on structural measures, the group who received the treatment showed significantly increased activation on fMRI in the posterior cingulate cortex (PCC)/precuneus and dorsolateral prefrontal cortex (DLPFC) bilaterally compared to the placebo group (**Figure 1**). An increase in rs-FRI was also noted after the treatment period in the treatment group only in the right PCC and the IPL of the default mode network (DMN). The DMN is a cortical network that has been shown to be active when the individual is at rest and deactivated when the individual is actively engaged in a cognitive task (86). Finally, increased rs-FC was noted in the treatment group only in the executive functioning network (left DLPFC) as well, which is implicated in active cognitive control during task performance. The increased activity in these networks was interpreted to be indicative of compensatory activation due to treatment effects. These authors also noted positive correlations between changes in rs-FC and cognitive performance, as well as changes on fMRI and cognitive performance, such that increased activation and increased rs-FC were each associated with improved task performance. This was observed across all subjects and when examining the treatment group only. Importantly, regions showing post-treatment changes in activity are areas known to be active in cognitively demanding tasks (87). Further analyses of the same data revealed increased rs-FC of the anterior

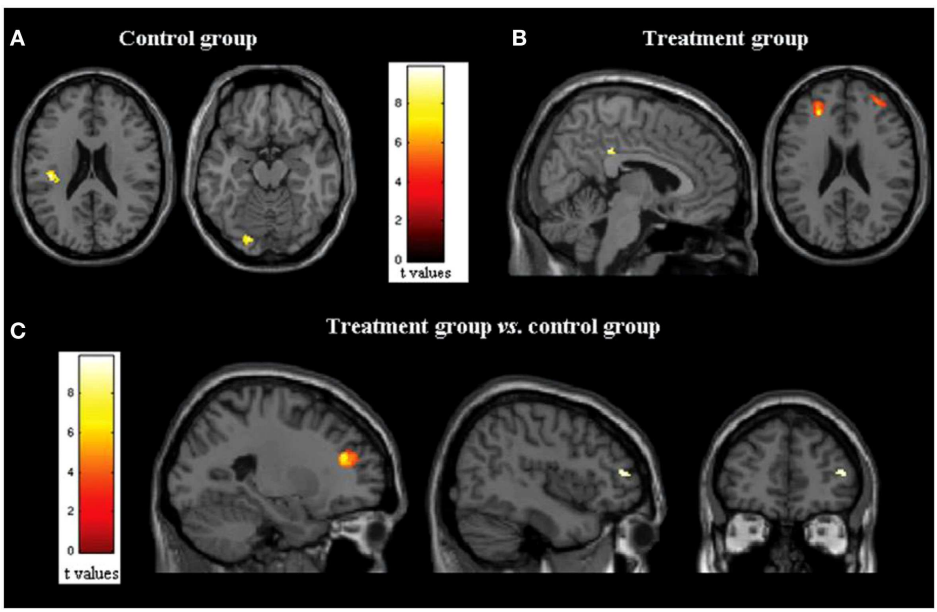

FIGURE 1 | (A,B) Statistical parametric mapping results (color-coded for *t* values) overlaid on high-spatial resolution T1-weighted MR images show changes in functional MR imaging activations during the Stroop interference condition in **(A)** control group (axial images) and **(B)** treatment group ($p = 0.05$, paired *t* test, family-wise corrected for multiple comparisons) (sagittal and axial images). **(C)** Statistical parametric mapping results (color-coded for *t* values) overlaid on high-spatial-resolution T1-weighted MR images show between group comparisons of functional MR imaging activations during the Stroop interference condition (analysis of variance, two-by-two factorial design; $p = 0.05$, family wise corrected for multiple comparisons) in treated group versus control group (sagittal and coronal images). Here and throughout, images are in neurologic convention (i.e., left side of the image shows left side of the brain, right side of the image shows right side of the brain). *Reprinted with permission from the Journal of Radiology.

cingulate cortex (ACC) as well as within the right middle frontal gyrus and the right IPL in the treatment group but not the control group (82). The control group showed decreased activation at follow-up in the ACC as well as the right cerebellum and the right inferior temporal lobule. In a follow-up investigation by the same group (88), rs-FC changes in the DMN following treatment predicted cognitive performance 6 months later. This indicates that the changes in patterns of cerebral activation and connectivity following cognitive rehabilitation can be maintained over time.

Also examining the RehaCom, Bonavita et al. (84) investigated changes in functional connectivity from before to after 8 weeks of cognitive rehabilitation with specific sections of the RehaCom program, namely, *Attention and Concentration*, *Plan a Day*, *Divided Attention*, *Reaction Behavior*, and *Logical Thinking*. They contrasted this treatment with a control group that received a placebo intervention. Post-treatment cognitive gains were noted in only the treatment group in processing speed abilities [symbol digit modalities test (SDMT) and PASAT] and verbal and visual learning and memory [(selective reminding test (SRT) and the spatial recall test (SPART-10/36)]. Changes were also noted in the DMN post-treatment, specifically increased FC in the PCC and IPC. In contrast to Filippi et al. (50), these authors failed to find a correlation between changes in FC and improvement in neuropsychological functioning.

Specifically focused on the neuroplasticity of the cerebellum, Cerasa et al. (53) demonstrated that specific, computer-based training for attention deficits results in adaptive neural plasticity of the neural network involved in attention. Specifically, they found increased activity in the posterior cerebral lobule (lobule IV) and the superior parietal lobule following RehaCom in the treatment group only. A significant relationship was noted between behavioral gains post-treatment and increased activation in these brain regions, similar to others (50). Interestingly, lobule VI of the cerebellum is active in the articulatory control system; the authors thus concluded the increased activation noted in this region post-treatment to represent an increased effort to subvocally refresh subvocal stimuli in this system.

Sastre-Garriga et al. (83) found increased brain activity in the cerebellum following a treatment designed to target attention, speed of information processing, executive functions, memory, and higher level language processes. Participants who completed treatment demonstrated improvement in cognitive performance as well as increased brain activity in the anterior and posterior lobes of the right cerebellum. Although suffering from some methodological limitations, the authors were able to conclude that the positive impact of the cognitive rehabilitation on cognitive performance may, in fact, be mediated by increased activity within the cerebellum, a finding further supported by Cerasa et al. (53). Although the cerebellum is a largely understudied brain region as it relates to cognition and cognitive rehabilitation, it is important to note that two existing studies on cognitive rehabilitation in MS highlight the adaptive neuroplasticity of the cerebellum in response to a treatment for attention deficits. This is clearly a region ripe for future investigation.

Penner et al. (89) examined the effect of a 3- to 4-week computerized training program targeting selective attention in 11 patients with MS on patterns of cerebral activation on fMRI. Increased activation was seen post-treatment in MS patients with both mild and severe cognitive impairment in brain regions involved in attention, namely, the PCC, the precuneus, and the dorsal frontal cortex. Behavioral improvement correlated with the increased activation noted in these regions post-treatment. Although the lack of a control group in the study design was a limiting factor of this study, these data indicate that persons with MS can benefit from cognitive rehabilitation across the range of severity of cognitive impairment and neuroplasticity can be induced by cognitive rehabilitation procedures. Penner et al. (90) concluded that cognitive rehabilitation may enhance neuroplasticity in persons with MS and encourages the use of fMRI to enhance our understanding of the induced plasticity in persons with MS, as well as identify effective cognitive rehabilitation protocols.

Although limited in number, the two existing studies examining the cognitive rehabilitation of memory functioning in MS via neuroimaging techniques, also support the existence of induced neural plasticity in response to treatment. Chiaravalloti and colleagues utilized both fMRI (78) and FC (79) to evaluate a 10-session cognitive rehabilitation protocol specifically targeting new learning and memory abilities through a randomized clinical trial. After treatment, greater activation was evident only in the treatment group during performance of a memory task within a widespread cortical network involving frontal, parietal, precuneus, and parahippocampal regions (**Figure 2**). In a separate analysis by the same group (79), a significant increase in FC was noted in the treatment group post-treatment between the left hippocampus and cortical regions involved in memory functions, namely, the left insula, right parahippcampal gyrus, right insula, precentral gyrus, and post-central gyrus (**Figure 3**). These changes were not seen in the placebo-control group. These results demonstrate the neuroplasticity of the memory network in response to cognitive rehabilitation targeting learning and memory deficits in MS.

Ernst et al. (81) also examined the neuroplasticity associated with memory abilities, examining changes on fMRI following treatment focusing on autobiographical memories in an MS sample. The authors define autobiographical memory as the "capacity to relive detailed events, evoking spatiotempoal context, in which they were encountered as they are remembered." The authors noted that following an intervention program for autobiographical memory, patients showed greater recruitment of the right cuneous, the left inferior and superior occipital gyri, the left precuneus and part of the lateral temporal cortex, largely on the left side, as compared with before treatment. These regions were consistent with regions known to be involved in the trained constructs. That is, changes were noted in posterior cerebral regions, known to be associated with the mental visual imagery trained in the training protocol applied. Significant improvement was noted in autobiographical memory, although the relationship between the behavioral and neuroimaging changes was not examined. Taken together, the two existing studies examining the efficacy of memory interventions in MS with neuroimaging both demonstrate increased activation in similar brain networks known to be integral to the trained function.

fMRI is thus a valuable tool to identify areas of dysfunction, and provides substantial evidence of both natural and induced neuroplasticity in persons with MS. Neuroplasticity in MS appears to

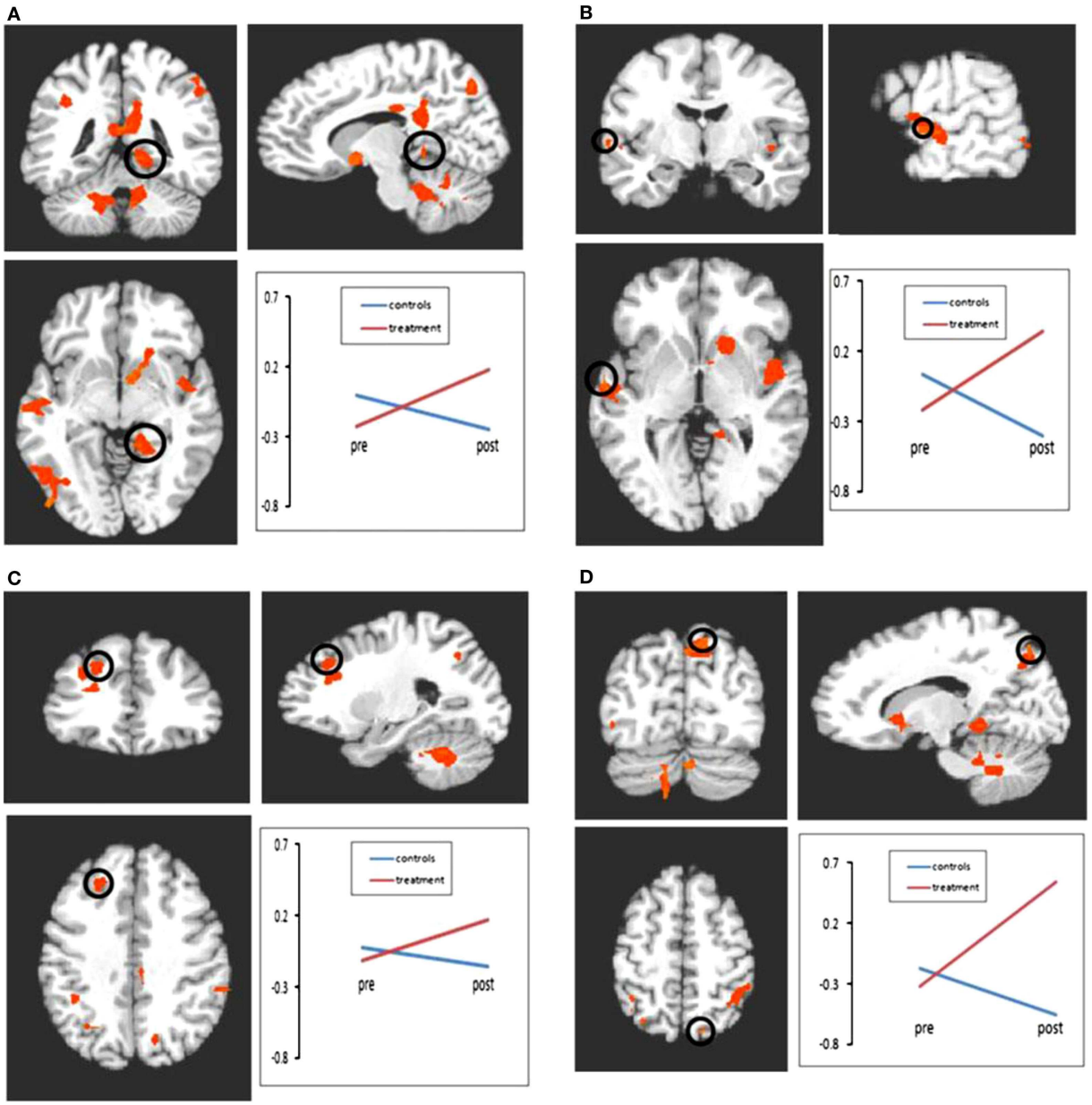

FIGURE 2 | Results of the 2 × 2 ANOVA with factors of time and group. Following treatment, significant increases in activation were seen in the treatment group relative to the control group in regions including frontal lobe, parietal lobe, and cerebellum. All comparisons are significant at $p < 0.01$ (minimum cluster size = 10 voxels). **(A)** Bold activation change from pre- to post-treatment in parahippocampal gyrus. Control group represented by blue line; treatment group represented by red line. All interactions shown are significant at $p < 0.01$. **(B)** Bold activation change from pre- to post-treatment in superior temporal gyrus. **(C)** Bold activation change from pre- to post-treatment in middle frontal gyrus. **(D)** Bold activation change from pre- to post-treatment in precuneus. *Reprinted with permission from the Journal of Neurology.

largely be adaptive in nature when in response to rehabilitation, minimizing the clinical consequences of the neurological injury. It seems that a positive outcome of cognitive rehabilitation is likely the presence of post-treatment changes in fMRI, indicating the strengthening of existing regions and pathways associated with the treated domain. The application of neuroimaging measures to examine the functional and structural basis of changes in cognitive performance following cognitive rehabilitation will enhance our ability to identify the most effective treatments for persons with MS and modify such treatment to achieve maximal efficacy (91–93).

INCREASED ACTIVATION/CONNECTIVITY: ADAPTIVE OR MALADAPTIVE?

Increases in cerebral activation, as well as increased functional connectivity can occur in persons with MS under varying conditions

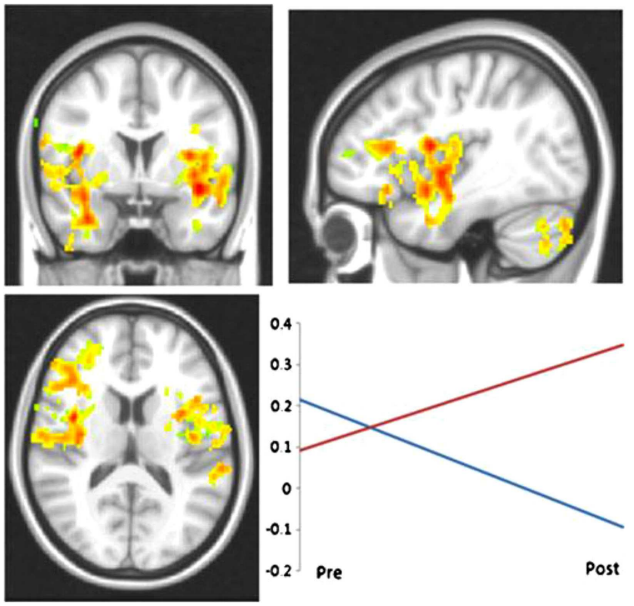

FIGURE 3 | LHIPP seed: increased connectivity between from LHIPP to left and right insula in the treatment group at post-treatment. Interaction plot displays increased connectivity to left insula. *R*-values are plotted on the ordinate; time is plotted on the abscissa. Red line indicates treatment subjects, blue line indicates controls. *Reprinted with permission from Brain Imaging and Behavior.

[see (94) for a complete discussion]. The first condition involves "local expansion." The term "local expansion" refers to an increase in activation in the region immediately surrounding the lesioned area or area affected by the disease (95, 96). Specifically, persons in the early stages of MS have been shown to demonstrate increases in activation and connectivity, as compared with healthy controls, in the absence of cognitive impairment. Such changes in brain function are often associated with intact cognitive functioning and interpreted as adaptive neuroplasticity. For example, Forn et al. (70) demonstrated increased cortical recruitment during fMRI, reflecting the local expansion of activation, in cognitively preserved CIS patients (70) suggesting that early cortical changes may, in fact, limit the clinical expression of neuronal damage resulting from MS. Audoin et al. (69) similarly showed that CIS patients exhibited significantly greater activation in the regions *normally involved* in executive functioning: orbitofrontal regions, right cerebellum, and bilateral lateral prefrontal cortex (PFC) region during the PASAT, as compared with healthy controls, suggesting this activation to be adaptive. Amann et al. (97) examined the cerebral activation patterns associated with a working memory fMRI task in RRMS subjects with mild cognitive impairment and healthy controls and found that the overall pattern of brain activation was similar between the two groups. However, in the Anmann et al. study, persons with MS showed local expansion of cerebral activation during task performance within regions typically associated with working memory (i.e., anterior frontal and inferior parietal cortex). Similar findings were observed by Forn et al. (72) in an early RRMS sample. Taken together, these studies indicate that the maintenance of cognitive performance was due to the local cerebral expansion, interpreted as adaptive plasticity. Thus, in both CIS patients (69, 70) and patients with early RRMS (72, 97), there are indications of early plasticity of cognitive processes. While task performance is intact, the minimal additional recruitment typically seen in local expansion of activation appears to be an active and effective compensatory mechanism occurring early in the disease process.

A second condition is one in which we observe "homologous area adaptation." Homologous area adaptation involves activation in areas in homologous regions of the contralateral hemisphere to the area impacted by disease (98, 99). In these instances, increases in cerebral activation/connectivity are correlated with *impaired* cognition. Chiaravalloti et al. (54) examined a modified PASAT administered via fMRI in three groups: MS with working memory impairment, MS without working memory impairment, and healthy controls. The healthy control group and MS group without working memory impairment showed a comparable activation pattern, i.e., primarily left hemisphere activation during working memory performance. However, in those MS individuals with working memory impairment, significantly more activation was noted bilaterally in the parietal and frontal regions in the MS group (indicative of both local expansion and homologous area adaptation). Further, the degree of extension of activation into the homologous right frontal region was correlated with *worse* cognitive performance, indicative of maladaptive neuroplasticity. This same pattern of results was also observed by Hillary et al. (55) on a different working memory task, with these authors interpreting their findings as indicative of neural inefficiency. Loitfelder et al. (100) compared HC with subjects with CIS, RRMS, and SPMS on a Go/No-Go task using fMRI and demonstrated that SPMS subjects showed activation in regions other than the task-related network observed in healthy controls (i.e., terms "extra-region" recruitment). The authors interpreted the observed extensive activation as neural inefficiency (100). Taken together, these several studies demonstrate cortical recruitment of "extra-regions" to support task completion, but this "extra-region" activation is associated with poorer cognitive functioning, and thus reflects maladaptive plasticity.

A final condition is one in which one observes increased activation in regions associated with the cognitive constructs being addressed within the treatment. This is precisely what is observed following cognitive rehabilitation. Multiple authors have shown increased activation of existing networks underlying trained functions in person with MS following treatment (78, 81). However, these areas are those known to underlie the performance of the skills taught during the active interventions. It thus appears that cognitive rehabilitation may not entail a traditional expansion of active brain regions into local or distal regions. In contrast, what appears to be occurring is increased activation of brain regions engaged by the techniques taught in treatment. This may be a strengthening of existing areas of activation or, in some cases, may involve newly activated regions. As an example, in Chiaravalloti et al. (78), increased activation was observed in the parietal regions during a verbal learning task. However, this activation is

directly related to the techniques taught in treatment – visualization. This is thus activation supporting newly engaged cognitive processes that were shown to support the successful completion of the task.

In conclusion, increases in activation/connectivity are seen in persons with MS following cognitive rehabilitation and these increases are often associated with improvement in the targeted cognitive domain. While increased activation has been found with increased cognitive decline and disease progression in studies of the natural progression of MS, it is important to note that this increase in activation due to disease progression is distinct from the activation observed following cognitive rehabilitation. Thus, there are situations in which increased activation and/or connectivity is a negative consequence of the disease. In these situations, the activation we are observing might be best termed "maladaptive compensation." That is, these extra areas of activation (or connectivity) are actually associated with worse performance and are therefore maladaptive (54, 55, 77). However, there are also situations in which such increases in activation and connectivity are positive, such as following effective cognitive rehabilitation. In these cases, the increased activation is associated with improvement in cognitive functioning and can thus be concluded to be adaptive. It is important to note that adaptive and maladaptive cerebral activation have been shown in the various disease stages (CIS, RR, SPMS). However, the documentation of cerebral reorganization via fMRI following cognitive rehabilitation has largely focused on RRMS patients to date. Thus, additional research is needed on cerebral reorganization after cognitive training, focusing on all MS phenotypes.

In reviewing the existing research, it is clear that there is significant neuroplasticity of cognitive functions in individuals with MS. Homologous region adaptation, local activation expansion, and extra-region recruitment all occur in an effort to maintain cognitive functioning. While much of this neuroplasticity is adaptive, it is important to note that in many situations, such neuroplasticity may be maladaptive, particularly in individuals that are demonstrating significant cognitive impairment and/or with disease progression. This maladaptive neuroplasticity (e.g., extra-region recruitment) may come at the cost of other cognitive functions for which the new areas now being utilized were crucial, such as processing speed. It is encouraging that such neuroplasticity can be induced through treatment such as cognitive rehabilitation, in an effort to "normalize" brain function and behavioral output. Moving forward, a focus on identifying adaptive versus maladaptive neuroplasticity associated with specific cognitive rehabilitation programs within all MS phenotypes would aide in the validation of the most effective cognitive rehabilitation interventions for persons with MS.

AUTHOR CONTRIBUTIONS

Dr. NC led the literature review, synthesis of the literature, and drafted the manuscript. Dr. HG assisted with synthesis of the literature and edited the manuscript several times. Dr. JD assisted the literature review, synthesis of the literature, and editing of the manuscript.

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Measuring gray matter and white matter damage in MS: why this is not enough

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INTRODUCTION

Over the past years, progress in cerebral magnetic resonance imaging (MRI) technology has increased the possibilities to quantify MS-related tissue changes, starting from lesion assessment in the white matter (WM) to the quantification of microstructural changes of the whole brain (1). This was expected to give full insight into the causes of MS patients' deficits but despite all achievements, the current plethora of MRI metrics still provides no complete explanation for the clinical condition on a group (2) and even less so on an individual level. However, within the scope of personalized medicine, this remains an important goal to better understand and ultimately minimize the functional impact of MS-related tissue damage.

In this context, functional cerebral changes including adaptation and plasticity are strong contributors to the apparent clinical consequences of MS and are likely to explain part of the "morphological-clinical gap" (3), notwithstanding ongoing controversies what patient deficits to consider and how to assess them. Against this background, we critically review the development and current state of techniques to assess gross MS-related morphologic damage and their contribution to understand the clinical consequences of MS (disability, and also cognitive problems and fatigue) and the obvious modulating roles of cerebral adaptation and plasticity as unraveled by functional MRI (fMRI). From existing data, we suggest that it is unlikely to ever achieve a satisfactory level of explanation and prediction of an individual patient's condition-based solely on morphologic information, although such insights might be better suited to define disease progression than clinical assessment.

WHITE MATTER DAMAGE IN MS

MS has traditionally been viewed as multifocal WM disease, and depicting lesions disseminated throughout the CNS using conventional MRI has become indispensable in early diagnosis and management (4). However, T2-weighted MRI lacks pathological specificity (5).

FOCAL WHITE MATTER PATHOLOGY

While the basic features of MS pathology constitute inflammation, demyelination in WM and GM, and diffuse neurodegeneration within the entire CNS, the individual components of the pathological spectrum vary quantitatively between early relapsing and late progressive MS (6). Moreover, remyelination of existing lesions may be extensive in a subset of patients and fail in others (6). All these components cannot be sufficiently assessed on T2-weighted MRI.

Compared to T2-hyperintense lesions, so-called "black holes" (severely and persistent hypointense lesions on T1-weighted MRI) have been shown to offer a more specific marker of matrix destruction and axonal loss (7). However, their definition is variable and strongly dependent on scanning parameters, which prohibits closer quantitation.

NON-CONVENTIONAL MRI TO QUANTIFY LESIONAL WHITE MATTER DAMAGE

A more refined insight into the composition of lesions may be gained by non-conventional techniques like magnetization transfer (MT) imaging (MTI), diffusion-weighted imaging (DWI), and diffusion tensor imaging (DTI).

MT-ratio (MTR) changes may precede the formation of active MS lesions by months, indicating changes in the macromolecular composition of pre-lesional WM long before a lesion becomes visible on conventional MRI (8). Once a lesion has formed, i.e., becomes apparent on T2-weighted MRI, MTI may serve to follow the evolution and fate of affected parenchyma. Comparison with histopathology has shown good correlations with both demyelination and remyelination, and also just with fiber or neuronal density (5, 9). In a longitudinal trial, MTR-changes followed different temporal evolutions and were ongoing in different lesion regions for at least 3 years after lesion formation (10).

Diffusion-weighted imaging and DTI yield different insights. Diffusion measures the microscopic Brownian motion of water molecules, which is hindered by cellular structures (e.g., cell membranes and axonal cytoskeletons). In general, low-fractional anisotropy (FA) and high-mean diffusivity (MD) are found in MS lesions, but values are highly heterogeneous. Unfortunately, few studies investigated pathological correlates of DWI in MS. Surprisingly, at post-mortem, MD and FA correlated more strongly with myelin content than with axonal count and gliosis in one study (11).

NON-CONVENTIONAL MRI TO QUANTIFY DIFFUSE WHITE MATTER DAMAGE

Diffusion-weighted imaging/DTI and MTI played important roles in shaping the notion that MS not only consists of focal

T2-lesions but also affects WM in a more widespread manner. Thus, normal appearing white matter (NAWM) in MS, in fact, is not normal, but demonstrates subtle microstructural abnormalities outside lesions. Histogram analyses have frequently been used to explore respective MRI metrics across the whole brain (12–14). Using MTI, MS patients consistently showed both lower average MTR and lower peak height (15) and respective DTI analyses demonstrated higher average MD, lower histogram peak height MD, and lower average FA (14, 16) compared to healthy controls, respectively. Lower FA values close to and higher values far from MS lesions suggest Wallerian degeneration (17), but MD and FA of NAWM only partially correlate with the extent and severity of focal lesions, indicating other factors like astrocytic hyperplasia, patchy edema, perivascular infiltration, demyelination, and axonal loss also contribute to such abnormalities (14).

STRATEGIC LOCATION OF WHITE MATTER DAMAGE

Assessing the strategic location of WM damage using lesion probability maps (LPM) or diffusion-based tractography (DBT) represents another promising approach to improve upon morphological-clinical correlations. Thus, LPM in different MS phenotypes revealed associations between specific neurologic and cognitive deficits with lesion accumulation in distinct, anatomically plausible, regions, but only to limited extent (18). Using tract-based spatial statistics [TBSS; a fully automated, whole-brain diffusion analysis method (14)] to identify loci where reduced WM-tract FA predicted impaired cognitive performance in MS patients, cognitively relevant tract localizations only partially overlapped with areas of high-lesion probability, but identified tract localizations were found to interconnect cortical regions involved in cognitive processing (19). Thus, there is evidence that abnormalities in strategic brain WM tracts contribute to cognitive impairment in MS, but the identified regions vary between studies and it is unlikely that such analyses could be performed on an individual level.

GRAY MATTER DAMAGE IN MS

GRAY MATTER PATHOLOGY

Autopsy studies have demonstrated that MS is also associated with focal lesions in and diffuse demyelination of GM (20, 21). The depiction of these kinds of MS-related damage has been and still is a challenge for MRI.

FOCAL GRAY MATTER DAMAGE

Intrinsically, low-myelin densities in the cortex (where demyelination generates little contrast), the often small size of lesions, and partial volume effects of cerebrospinal fluid impede the detection of cortical GM lesions on conventional MRI (21). Introduction of the double-inversion recovery (DIR) sequence with superior sensitivity compared to T2- and fluid-attenuated-inversion-recovery (FLAIR) sequences improved this situation, but post-mortem comparison showed that 80% of lesions still remain undetected (20, 21). Interestingly, MRI-visible cortical lesions do not differ from MRI-invisible lesions in their pathological profiles (20). Combination with other sequences such as phase-sensitive inversion recovery and T1-weighted 3D-spoiled gradient-recalled echo and ultra-high-field scanners might help to partly overcome these problems (20, 22), but this approach is not realizable in clinical settings. Importantly, despite representing the commonest lesion type, subpial cortical lesions largely escape detection by MRI (20). Deep GM pathology is somewhat easier to depict than cortical GM pathology as lesions in deep GM structures, spinal cord, and hippocampus are generally mixed GM/WM lesions and slightly more inflammatory (21).

DIFFUSE GRAY MATTER DAMAGE

Cortical thickness is reduced in MS (23) and a mean cortical thinning of 10% has been found independently of cortical lesions, suggesting mechanisms besides cortical demyelination contribute to cortical atrophy (21). A recent study combining post-mortem imaging and histopathology to explore the underpinnings of cortical atrophy identified neuronal density, neuronal size, and axonal density as predictors of cortical GM volume in long-standing MS (24). GM constitutes about 65% of brain parenchymal tissue, and atrophy of GM largely drives whole-brain atrophy in MS (20). GM atrophy in MS occurs both at global and regional level and can be quantitated using MRI. It also does not directly correlate with the number of WM lesions and diffuse NAWM damage, suggesting partially independent pathological processes (22). Unfortunately, GM volume measures are inherently non-specific and reveal little about the exact cause of tissue injury (20).

NON-CONVENTIONAL MRI TO QUANTIFY GRAY MATTER DAMAGE

Analogous to but less frequent than respective WM studies, DWI/DTI and MTI have also been used to quantify GM damage in MS. Consistent with differences in pathology, DTI detected higher MD and FA in cortical lesions than in WM lesions of MS patients (22). New approaches to study cortical MTR changes include segmentation of the cortex to obtain separate information on outer and inner bands, where the lowest outer cortical MTR was seen in secondary progressive MS, consistent with post-mortem findings of more extensive subpial pathology in this group (25).

STRATEGIC LOCATION OF GRAY MATTER DAMAGE

Extensive GM involvement has been associated with cognitive decline, motor deficits, fatigue, painful syndromes, and ocular motility disturbances in MS. In this respect, the thalamus has been highlighted, as it relays sensory information to higher cortical centers that influence cognition (26). A strategic significance has also been demonstrated for the hippocampus, as lesions in this area strongly correlate with impaired visuospatial memory and processing speed (20, 21). Further, using LPMs of DIR images, cortical MS lesions have been demonstrated to be mainly distributed in the frontal and temporal lobes, with prominent involvement of motor and anterior cingulate cortices (27).

CONTRIBUTION OF WHITE AND GRAY MATTER DAMAGE TO EXPLAINING CLINICAL DEFICITS

All the above techniques have greatly enhanced our understanding of the complexity of MS tissue damage and provide possibilities to assess the structural changes

associated with MS in ever more detail. At group level, several discussed metrics alone or in combination have shown good correlation with measures of disability or cognition [e.g., Ref. (28)] and even simple MRI markers appear to be an excellent surrogate for treatment response (29). However, these complex insights have not transformed into a sufficient capacity to explain or even predict a patient's functioning and clinical deficits, and are far from having reached utility in daily clinical practice. We suggest that the reasons for this are not only the complexity of MS-related damage – which is certainly even much greater than addressed above (e.g., consider the role of other CNS compartments such as the spinal cord) – but rather the individual variability in processes of plasticity and adaptation.

FUNCTIONAL MRI AS ONE APPROACH TO GAIN FUNCTIONAL INFORMATION

Functional MRI studies of visual, cognitive, and motor systems consistently demonstrated functional changes in all MS phenotypes, characterized by altered activation of regions normally devoted to performance of a task or recruitment of additional areas compared to healthy subjects (3, 22, 30, 31). Given the correlation between functional and structural abnormalities (30), the former appear to partly limit the functional consequences of structural damage in MS. fMRI abnormalities already occur in CIS, but differences in activation patterns between phenotypes are striking (32, 33), suggesting profound changes in the functional organization of the MS brain with disease progression. Final exhaustion of adaptive capacity may constitute one key factor for unfavorable clinical evolution or cognitive decline, although the decisive factors driving transition from adaption to maladaptation are unknown. However, maladaptation in MS is not only the consequence of the final exhaustion of adaptive plasticity but it may also be expressed in early stages of the disease as enhanced functional connectivity (34). While patients with "long-term low disability MS" may functionally withstand considerable amounts of brain tissue damage, others already suffer from severe disability (35). Individual differences in brain reserve and cognitive reserve thereby might play a role (36–38). Combining MRI measures of structural damage with those of abnormal functional and structural connectivity (3) using resting state fMRI (13, 39) appears promising to further elucidate such relationships at group level, but this would necessitate prospective longitudinal studies (40) with long-term follow-up, ideally in multi-center settings (41).

CONCLUSION AND FUTURE DIRECTIONS

Despite increasing level of detail, morphological insights using MRI by nature only allow assessment of (micro)structural disease-related processes in MS-brains. fMRI enabled detection of paralleling adaptive cerebral changes, which – besides the stage and dynamics of the disease – most likely are also modulated by individual differences ("functional reserve"). Interpretations of such changes are corroborated and usefully augmented by concomitant assessment of morphological MRI changes. Yet, measurement of brain damage by structural MRI alone clearly does not suffice to comprehensively appreciate the consequences of the disease, although it is ideal for specific questions (e.g., assessment of disease activity, remyelination, or evolution of atrophy). To better understand mechanisms of functional adaption in MS, longitudinal studies including (micro)structural and functional MRI in large registries of early MS followed for many years are needed. Whether this will finally allow judging capacity for adaption at the individual level remains unclear.

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Clinical implications of neuroplasticity – the role of rehabilitation in multiple sclerosis

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Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) that preferably affects young adults and causes a multitude of symptoms including visual disturbances, spasticity, weakness, impairment of walking, coordination difficulties, tremor/ataxia, sensory problems, and bladder disturbances. In addition, "invisible" symptoms such as fatigue, depression, and cognitive dysfunction are also common and may even be present early in the course of the disease (1). These symptoms often cause huge disability and have an impact on family, social, and work activities. Despite the advances of pharmacological treatment, particularly by disease-modifying therapies, the majority of MS patients accumulate new lesions and disabilities along the disease course and thus, there is a continuing need for comprehensive, multidisciplinary treatment, which constitutes the basic concept of rehabilitation (2).

Rehabilitation is defined as a "problem-solving educational process aimed at reducing disability and handicap experienced by someone as a result of disease or injury" (3). The primary goal is to reduce the limitations of activity and participation in order to achieve the highest possible level of independence and to increase and maintain quality of life of MS patients (4). With respect to the large variety of symptoms, a multidisciplinary approach is required for MS rehabilitation that includes physiotherapy, occupational therapy, cognitive rehabilitation, psychological therapy, speech therapy, measures for improving fatigue, and coping programs (2, 5). These measures facilitate the reorganizing mechanisms within the CNS and therefore, rehabilitation may be regarded as "applied neuroplasticity." This article gives an overview of the most recent scientific evidence and measures of MS rehabilitation, and the relationship between neuroplasticity and functional improvement in MS.

MULTIDISCIPLINARY REHABILITATION IN MS

There is a large interest in scientifically sound studies dealing with the effectiveness of neurorehabilitation. During the last decades, a growing body of research has been performed, mainly in stroke patients, but also in MS. A recent update of a Cochrane review identified 10 randomized controlled trials dealing with multidisciplinary rehabilitation in MS (6). Although data are limited, the available evidence suggests that inpatient rehabilitation may have short-term effects on activity and participation, but not on impairment. Furthermore, there was "moderate evidence" to support inpatient or outpatient rehabilitation programs to improve disability, bladder dysfunction, and participation that may last up to 12 months. Since these effects diminish with time (7), repetition of multidisciplinary rehabilitation seems necessary, preferably on an annual base.

PHYSIOTHERAPY AND EXERCISE THERAPY

Physiotherapy is one of the basic methods of MS rehabilitation and aims at improving motor function, stability of gait, and walking capabilities. Moreover, endurance and physical fitness may also be strengthened and thus, fatigue may be ameliorated. There are many techniques and methodologies based on neurophysiological concepts (i.e., Bobath, Vojta, Brunkow, and proprioceptive neuromuscular stimulation) as well as newer approaches such as equipment-supported training, treadmill exercises, robot-assisted gait training, and constraint-induced movement therapy (CIMT) (2). Neither of these techniques has shown superiority about another which means that the appropriate method should be chosen according to the capabilities and disabilities of the individual patient, but also to the knowledge and resources of the rehabilitation team. Physiotherapy may also improve breathing dysfunction and bladder disturbances by using training programs specifically directed toward respiratory muscle and pelvic floor function, respectively (2, 8).

In numerous studies, the beneficial effects of exercise therapy for persons with MS have been shown. Despite methodological problems (small sample sizes, heterogeneous groups of patients, different interventions), there is good evidence that exercise has positive effects on balance (9), mobility (10), muscle weakness (11–13), depression (14), and fatigue (15). Therefore, persons with MS should be encouraged to participate regularly in endurance and/or resistance training of low to moderate intensity. These interventions are well tolerated and not associated with side effects (16, 17), but could positively influence both, the limitations caused by the disease itself and the additionally deconditioning effects of an inactive lifestyle.

COGNITIVE DYSFUNCTION AND FATIGUE

Cognitive dysfunction often accompanies the symptomatology of MS and is not

necessarily associated with motor disability. It may occur early in the disease course and significantly affects employment, social life, and the activities of daily living (18). The most commonly affected areas are information processing speed, attention, memory, visuo-constructive performance, and executive functions (19). It is of utmost importance to recognize these problems as early as possible by appropriate neuropsychological tests, and to tailor the rehabilitation measures specifically toward the cognitive deficit. Since drug treatment is disappointing [the promising effects of the anti-cholinesterase agent donepezil could not be reproduced in a large randomized controlled trial (20)], treatment consists of neuropsychological training, provision of aids, and supportive psychotherapy [RIMS (21)]. Albeit with limited evidence, a systematic review indicated that cognitive training can improve memory span, working memory, and immediate visual memory (22). Moreover, benefits were found for specific trainings of attention, executive functions, learning performance, and memory (23, 24).

Fatigue is one of the most common and debilitating symptoms in MS and clearly different from normal tiredness. Patients suffer from feelings of lassitude and abnormal tiredness that may increase during the day as well as lack of energy and motivation, which all may impact activities of daily living and work ability [RIMS (21)]. The pathogenesis is still unknown and may involve different mechanisms such as lesions of cortical and/or subcortical motor pathways with involvement of motor cortex and basal ganglia, decreased energy metabolism in the frontal cortex, autonomic dysfunction, endocrine disturbances, and dysregulation of the hypothalamus–pituitary–adrenal axis [(25), RIMS (21)]. These "primary" fatigue needs to be differentiated from secondary mechanisms such as sleep disorders, anemia, and thyroid dysfunction, but also from depression and cognitive deficits. The subjective dimension of fatigue may be evaluated with standardized questionnaires, and attention tests of alertness may be an objective assessment method (26). Drug treatment is often not efficient. Therefore, management of fatigue consists of non-pharmacological measures such as counseling of patients and caregivers, structuring the day with regular breaks, energy management programs, cooling, specific neuropsychological training (attention), and exercise therapy (26).

NEUROREHABILITATION AS "APPLIED NEUROPLASTICITY"

Within the last years, our knowledge about the basic mechanisms that may be responsible for the restoration of neurological disabilities is rapidly increasing. It is now generally accepted that even the mature brain can undergo plastic changes (27). Although the majority of studies are dedicated to the dynamic reorganization of the motor system after an acute event, i.e., stroke (28), these neuroplastic changes may also occur in a chronic disease as it is MS. For instance, brain activation was exaggerated in MS patients with normal motor function compared to healthy controls by using a finger tapping paradigm (29). The brain activation pattern changes with both, increasing diffuse brain injury (assessed by relative *N*-acetylaspartate concentration, a marker of axonal integrity) and increasing hand disability, and was present during active as well as passive finger movements reflecting true brain reorganization (30). The same applies for cognitive function: while MS patients in the early stages of MS performed similarly to healthy controls on clinical outcomes and the visual analog of the Paced Auditory Serial Addition Test (PASAT), brain activation was increased in the patient group indicating that compensatory adaptive mechanisms (i.e., neuronal plasticity) may be present very early in the course of MS (31).

Zeller et al. tried to elucidate the basic mechanisms underlying neuronal plasticity in MS. For this purpose, rapid-onset central motor plasticity was assessed in 22 patients with moderately severe, stable MS and compared to healthy controls using paired associative stimulation (PAS), a protocol that models long-term synaptic potentiation in the cerebral cortex and that combines repetitive electric nerve stimulation with transcranial magnetic stimulation (TMS). In contrast to the above mentioned studies, MS patients performed worse in clinical and paraclinical tests of motor function, but the enhancement of corticospinal excitability and the training-induced increments of motor performance were similar to controls. PAS-induced plasticity and motor learning did not correlate with motor impairment or CNS injury. Based upon their findings, the authors concluded that the early steps of neuronal plasticity are unlikely to limit the extent of compensatory changes in MS and therefore, rehabilitation efforts should focus on mechanisms supporting the later stages of motor learning (32).

An intriguing question of current research is whether rehabilitation procedures may induce and/or support compensatory adaptive changes. In this regard, evidence albeit limited is available that the clinical improvements of both, motor and cognitive rehabilitation, correlate with neural plasticity in the CNS of MS patients. Sastre-Garriga et al. investigated 15 MS patients and 5 healthy controls by functional magnetic resonance imaging (fMRI) with the PASAT paradigm. The cognitive rehabilitation program consisted of 15 computer-supported sessions and 5 non-computer-supported cognitive stimulation group sessions. After 5 weeks of cognitive training, patients showed significant clinical improvement of their neuropsychological performance, and this correlated to increased brain fMRI activity in several cerebellar areas (33). In a double-blind, randomized controlled trial of 12 MS patients, computer-assisted cognitive rehabilitation of attention deficits increased fMRI activity in the posterior cerebellum and in the superior parietal lobule in parallel to enhanced performance in attention abilities compared with 11 age- and gender-matched MS patients receiving a placebo intervention (34). Similarly, visuomotor performance improved after the first practice session of a visuomotor task (short-term practice) and after 2 weeks of daily sessions of the same task (longer-term practice) in both, 23 MS patients and 12 healthy controls. However, different relationships between the improvements of function and fMRI activity were found between the groups: in MS patients, increased function was associated with lower activation in the sensorimotor, posterior cingulate, and parahippocampal cortices, whereas in controls, greater long-term improvements correlated with smaller activation reductions in the visual cortex supporting the notion that even in MS patients with a high burden of pathology, brain plasticity is preserved, and that cognitive

systems different from those of healthy controls contribute to this plasticity (35). However, despite the promising results that rehabilitation may indeed cause not only clinical improvement of cognitive and motor performance but also has distinct effects on brain activation, the role of fMRI in the context of clinical neurorehabilitation needs to be elucidated.

When summarizing the above mentioned findings, there is little doubt that plastic changes occur in the CNS, and that these changes may be modulated by practice. From a clinical point of view, it is obvious that patients undergoing neurorehabilitation improve with practice. Thus, these observations may bridge the gap between basic science and clinical experience. The results from basic studies may provide the scientific rationale to investigate recovery-oriented strategies in clinical trials and to implement them into rehabilitation measures. Several promising new rehabilitation techniques are examples of this approach: impairment-oriented training, CIMT, electromyogram-triggered neuromuscular stimulation, and robotic interactive therapies (2). It should be kept in mind that most of this evidence came from studies in patients with stroke or spinal cord injuries. However, more and more studies support the usefulness of these measures also in MS patients that reflect the clinical experience that we have made in our rehabilitation center during the last years (5). High-quality, carefully designed studies of the effectiveness of neurorehabilitation are necessary that should include both, clinical outcomes and neuroplastic measures. These studies may further move MS rehabilitation from empirical strategies toward evidence-based interventions and help to elucidate the basic mechanisms that are responsible for the clinical effects. Eventually, further research may provide the base to develop effective therapies that support the neuroplastic changes responsible for functioning, activity, and participation of persons with MS in order to reach and maintain their optimal physical, sensory, intellectual, psychological, and social functioning levels and promote the best possible quality of life.

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