

# Neurorehabilitation in persons with multiple sclerosis: scientific basis and options of treatment

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## Abstract

**Introduction:** Multiple Sclerosis (MS) is the leading cause of non-traumatic disability in young people. Nowadays, neurorehabilitation is commonly prescribed in patients with MS, but there are still some issues to be explored further. In this review, we discuss the following topics: 1) the neuroscientific basis of neurorehabilitation in MS; 2) what would be the ideal set of rehabilitative treatment. Inpatients, outpatient or home-based therapy? **METHODS:** A systematic search was made, using combination of the following terms: rehabilitation, multiple sclerosis, disability, plasticity, motor learning, cognitive rehabilitation, quality of life.

**Results:** A growing amount of evidence suggest that motor and cognitive rehabilitation may enhance functional and structural brain plasticity in patients with MS. Improvement of function seem to be correlated with functional Magnetic Resonance Imaging changes in brain. Moreover, several studies show the effectiveness of cognitive rehabilitation to improve some domains of neuropsychological functions, such as attention, information processing and executive functions.

Regarding the rehabilitative setting, it should be chosen taking into account the personal needs of each patient. All the studies, performed in different setting, demonstrated the effectiveness of rehabilitation in MS patients.

**Conclusions:** Rehabilitation is effective in mitigating disability and improving QoL in persons with MS. Nevertheless, it is urgent a consensus on the unsolved matters such as outcome measures, cost/effectiveness over a long period and suitable sets in which people with MS should be allocated.

## Introduction

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease of the central nervous system. Approximately 2.5 million persons are affected worldwide [WHO 2004] [1]. In young adults, MS is the leading cause of non-traumatic disability. The impact on the Health Related Quality of Life (HRQoL) can be very heavy and dramatic [2-6].

MS is a disease with a remarkable heterogeneity in clinical course, neuroradiological features and involvement of susceptibility gene loci. Patients typically present with either a relapsing or progressive disease course commonly defined by four clinical phenotypes: relapsing-remitting MS (RRMS), primary-progressive (PPMS), secondary-progressive (SPMS) and progressive relapsing (PRMS) [7].

The pathological processes involve several functional systems and consequently, the disability is a variegated world, in which the patient build up a multiplicity of neurological deficits. In addition, the disease has an unpredictable and progressive course, which aggravates the disability over the time [8,9]. The variety of MS impairments and the relative disabilities determine a comprehensive medical intervention, which could be only provided by multidisciplinary programmes [10]. Within these programmes, rehabilitation can be highly useful in person with MS (PwMS). While immunomodulating drugs aim to decrease exacerbations and slow down disease progression, rehabilitative intervention has mainly different goals, which can be shortly summarised: a) improving or maintaining general health; b) improving impairment of function such as loss of strength; c) minimising the effects of impairment such as spasticity; d) providing

adaptive strategies to minimise disability; e) providing adaptive equipment and devices, such as orthoses, canes and wheelchairs, in order to reduce functional dependence; f) training skills to improve vocational capabilities; g) giving counselling to enhance strategies of coping with the changes brought on by the disease; h) providing symptomatic management [11-16]. All these aims should be included within a multidisciplinary rehabilitation project. Lastly but not least, rehabilitation has to determine a positive impact on either mental or physical components of HRQoL [17].

For many physicians, neurorehabilitation is a difficult and fascinating challenge which, at first glance, may seem rather arduous and invincible. The first obstacle facing MS rehabilitation consists of the lingering scepticism of some neurologists, who are convinced of its relative ineffectiveness. Execution of clinical trials focused on the rehabilitation is difficult, because of the contrast between the habitually empirical philosophies of rehabilitation and the rules of evidence-based medicine. These difficulties are due to several factors, such as

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**Key words:** multiple sclerosis, rehabilitation, disability, quality of life, brain plasticity

**Received:** August 19, 2016; **Accepted:** September 29, 2016; **Published:** October 03, 2016

heterogeneity of MS patients, lack of control group, quantitative and qualitative disparity of rehabilitative intervention, and concomitant treatment with either disease modifying or symptomatic medications, lack of appropriate and sensitive outcome instruments.

The effects of rehabilitation on patients with MS were studied as early as the 50s [18-22]. However, the neuroscientific basis of neurorehabilitation are not completely established. Beside, the neural substrates underlying the recovery and the functional compensation are incompletely understood in MS.

This review will address the following questions:

- a) May motor and cognitive rehabilitation induce functional and structural plasticity into the brain of people with MS?
- b) What would be the most appropriate and effective set of rehabilitation in minimize impairment, reduce disability or improve HRQoL?

## Methods

A search was carried out, using combination of the following terms: rehabilitation, multiple sclerosis, disability, plasticity, motor learning, and quality of life.

The following databases were systematically searched: EMBASE (1974 to 2015), Medline (1950 to 2016) and PubMed (1950 to 2016). The number of studies was reduced removing those not primarily about MS and the duplicatas.

## Results

Since the 80s, many randomised controlled trials for rehabilitation in MS have been carried out and are summarised in Table 1 [13,23-40].

### Effects of exercise training

Several studies analysed the effects of the exercise training on impairment, disability and HRQoL of MS patients. Petajan et al. reported that ambulatory MS patients benefited from aerobic training in terms of fitness, reduced fatigability and improved QoL perception [24]. Freeman et al. [25] found a positive effect on disability as assessed by the Functional Independence Measure (FIM) and a negligible effect on impairment. The benefits gained from rehabilitation were partly maintained after discharge, despite worsening neurologic status [38]. With a chronic and progressive disease as MS, carry-over of benefits assumes a fundamental role. Patti et al. observed carry-over of benefits on disability for a further six weeks after a short outpatient treatment, without changing on impairment [29]. In the Solari et al. study, physical rehabilitation determined improvement in disability detected by the FIM motor domains and had a positive impact on mental components of HRQoL perception [27]. Khan et al. performed a stratified, randomised, waitlist controlled study over 12 months, in which an individualised rehabilitation programme reduced disability as measured by FIM motor domains, while there were no differences between control and treatment group as regard to participation and QoL [13].

A randomised controlled trial involving 36 patients highlighted that long-term light to moderate intense resistance training improved muscle strength (maximal isometric strength of both knee extensor and flexor muscles), but did not change dynamic muscle strength and functional mobility [34].

To summarise the evidence, we throw a look on the conclusions of

Cochrane Reviewers, issued in the last years.

For occupational therapy, no conclusions can be stated whether it can improve outcome in PwMS. This is partly due to the small number of included patients in the available studies, which evaluated an energy-conservation course for groups of patients and a counselling intervention. The results of the energy conservation studies were considered as biased because of the design used, whereas the randomised controlled study (RCT) on counselling did not report significant results [41]. A recent retrospective study concluded that inpatient occupational therapy improved FIM scores, exerting positive effect on functional performance in all categories except feeding, with significant correlation in upper extremity dressing and memory [42].

Conversely, there are strong evidence in favour of exercise therapy compared to no exercise therapy in terms of muscle power function, exercise tolerance functions and mobility-related activities. These findings were highlighted in the Cochrane Review, which selected nine high-methodological-quality RCT including 260 participants. No evidence was observed for exercise therapy on fatigue and perception of handicap [43]. Theoretically, persons with MS trend to reduce their physical activity, and this in turn could result in deconditioning across multiple multiple domains of physiological functioning. The resulting deconditioning feeds back and further drives physical inactivity until a threshold is reached that likely begins the progression of walking impairment. Therefore, there is a conceptual rationale for exercise training, which must be included in a rehabilitative project [44].

### Neuroscientific foundations of neurorehabilitation in MS

**Cortical reorganization:** Brain plasticity is the capacity of central nervous system to adapt to new environmental challenges or anatomical damage [45]. Brain changes after cognitive rehabilitation were evaluated by using structural and functional magnetic resonance imaging techniques (fMRI).

This plastic changes, such as axonal sprouting, collateral pathways circumnavigating lesions in descending motor tracts and cortical adaptation may underlie the functional compensation in MS [46-48]. Lee et al. demonstrated that cortical recruitment for simple movements can change both quantitatively and qualitatively in the sensorimotor cortex of MS patients. They hypothesized that cortical reorganization or “unmasking” of latent pathways could contribute to functional recovery [49]. The recruitment of additional cortical of the sensorimotor network was found to be confined to the controlateral hemisphere in patients with scattered white matter lesions and no previous symptom of motor deficit [50]. Besides, this further recruitment involved also the ipsilateral sensorimotor network in patients with a previous hemiparesis and a larger number of lesions specifically located along the corticospinal tract [50].

This cortical reorganization was also demonstrated in patients with Primary Progressive (PP) MS, who showed greater activation bilaterally in the superior temporal gyrus, ipsilaterally in the middle frontal gyrus, and, contralaterally in the insula/claustrum than health controls in fMRI during the execution of specific movement [51].

There are some other pieces of evidence in support of the adaptive changes involving reorganization of cortical representation in MS patients [52-57]. How this cortical reorganization responds to rehabilitative training has not been completely clarified. More specifically, the neural substrates underlying new skills acquisition and relearning of lost functions in patients with MS are poorly understood. In Morgen's study, patients with MS and health volunteers underwent

**Table 1.** Randomised controlled trials (RCT) in MS rehabilitation.

Main author Journal	Subjects	Conclusion
Francabandera <i>et al.</i> [23]	67 patients with chronic progressive disease followed over 3 weeks	Inpatient rehabilitation led to a significant reduction of disability as compared to outpatient treatment
Petajan <i>et al.</i> [24]	Fifty-four patients assigned to treatment or no treatment groups	Treated group improved in maximal aerobic capacity, upper and lower extremity strength, all component of the physical dimension of The Sickness Impact Profile.
Freeman <i>et al.</i> [25]	50 inpatient with progressive MS followed for 12 months after discharge	Improvement in disability , emotional well-being and physical component of QoL were maintained for a period from 6 to 10 months after discharge
Di Fabio <i>et al.</i> [26]	12 outpatient with chronic progressive were compared with 19 similar on a waiting list	Improvements in six health status measures on the Rand 36-Item Health Survey 1.0 (SF-36) in treated group. No improvement in the wait-listed group
Solari <i>et al.</i> [27]	27 ambulatory MS inpatient treated for 3 weeks versus 23 control MS patients	Treated patients improved in FIM motor domain and in overall HRQoL profile
Patti <i>et al.</i> [28]	58 outpatients assigned to the study treatment for 6 weeks and 53 to a waiting list	All SF-36 domains improved in treated group
Patti <i>et al.</i> [29]	58 progressive outpatient treated for 6 weeks, in comparison with 53 progressive patients in control group.	Improvement in disability (FIM) in treated group. No changes in control group. Benefits maintained for a further six weeks
Craig <i>et al.</i> [30]	20 patients with MS relapse were treated with both intravenous methylprednisolone and rehabilitation. They were compared with 21 patients with MS relapse, treated only with intravenous methylprednisolone	Patients treated with both steroids and rehabilitation showed significant differences in the Guy Neurologic Disability Scale, Amended Motor Club Assessment, Barthel Index, Human Activity Profile and SF-36
White <i>et al.</i> [31]	Eight MS subjects volunteered for twice weekly training sessions	Knee extension (7.4%), plantar flexion (52%) and stepping performance (8.7%) increased significantly
Rampello <i>et al.</i> [32]	Nineteen subjects with mild to moderate disability secondary to MS participated in a randomized crossover controlled study. Comparison between the effects of aerobic training and the effects of a neurological rehabilitation protocol	After the AT, significant increase in 3 MSQOL-54 scale scores After the NR program, significant improvements in 2 MSQoL54 and a significant reduction in emotional well-being scores.
Khan <i>et al.</i> [13]	49 in and out –patients were treated with an individualised rehabilitation programme for a mean duration of 34 days. They were compared with 52 patients allocated in a control waitlist group	Treated group improved in the FIM motor scores
Patti <i>et al.</i> [17]	Two treated group compared with control waiting list. Treated patients were divided into two groups: Group A outpatient, Group B inpatient	Both outpatient and inpatient groups showed significant improvement in FIM; only outpatient group improved in SF-36- No changes in control group.
Broekmans <i>et al.</i> [34]	11 patients were treated only with standardized light to moderately intense unilateral leg resistance training ; 11 patients with resistance training and simultaneous electro-stimulation.; 14 were allocated in control group	Maximal isometric knee extensor and knee flexor strength increased; dynamic muscle strength and functional mobility did not change; simultaneous electrostimulation does not further improve training outcome
Collett <i>et al.</i> [35]	Sixty-one persons with MS were randomised and treated with different exercise intensities.	Fifty-five patients were included in the analysis. Considering all participant, 6 weeks of cycling exercise produces benefits in mobility(2 min. walk) that were maintained with further sessions
Lozano-Quilliset <i>al.</i> [36]	Randomized and controlled single blinded study carried out by the use of RemoviEM, a system based on Kinect that uses virtual reality and natural user interfaces.	Significant group-by-time interaction was detected in the scores of the Berg Balance Scale and the Anterior Reach test in standing position. Post-hocanalysis showed greater improvement in the experimental group for these variables than in control group
Plow <i>et al.</i> [37]	Participants were randomized to receive the intervention immediately (n =14) or receive it at week 12 (n =16). Treatment consisted of home-exercise program and following up with customized pamphlets, which are matched to participants' stage of readiness to change physical activity behaviour and physical activity barriers	There were significant improvements in the immediate group compared with the delayed group in physical activity levels and health and function outcomes (Godin Leisure-Time Exercise Questionnaire, SF-12, Symptoms of Multiple Sclerosis Scale, and 6-minute walk test)
Rietberg <i>et al.</i> [38]	Forty-eight ambulatory MS patients with chronic fatigue were randomized to individually tailored, multidisciplinary outpatientrehabilitation or to MS–nurse consultation.	Primary outcome measure was the Checklist Individual Strength (CIS-20R), which showed no significant differences between groups at 12 weeks and 24 weeks.
Sangelajetal.[39]	RCT on 59 patients divided into the intervention (n = 39) and control groups (n = 20). The intervention group received 10 weeks of combination therapy including aerobic, strengthening, balancing and stretching exercises	Significant changes in the intervention group in comparison to the control group in the second phase of the study comparing to the first one for Berg Balance Test, Six-minute walking test and Fatigue Severity Scale
Straudi <i>et al.</i> [40]	24 subjects randomly assigned to high-intensity rehabilitative task-oriented circuit training (TOCT) over 2 weeks followed by a 3 months home exercise program, whereas control group did not receive any specific rehabilitation intervention	After TOCT walking ability and health-related quality of life were improved with minor retention after 3 months. The control group showed no significant changes in any variables.
Tyler <i>et al.</i>	Twenty chronic MS subjects with an identified gait disturbance were randomly assigned to either an active or control group. The therapy was based on the the effect of targeted physical therapy with and without cranial nerve non-invasive neuromodulation (CN-NINM), on the walking	Dynamic Gait Index scores improved for both groups. There were significant between-group differences, with the active group showing statistically greater improvement than the control group mean.

a motor training. Before training, motor tasks determined more prominent activation of the contralateral dorsal premotor cortex in patients than in controls. After training, unlike the control group, patients with MS did not exhibit task-specific reductions in activation in the contralateral primary somatosensory, motor and adjacent parietal association cortices. The main findings of this study were that motor training resulted in task-specific decreases in activation in contralateral cortical areas in controls but not in patients [57].

**Motor learning and rehabilitation:** Several studies highlighted improvements in upper limb function, gait or head control during variable lengths of training [58-62]. Some of these studies indicated that early in the disease, MS subjects have intact adaptive capabilities, while the ability to learn motor skills may be progressively impaired with higher levels of disability [58,59] especially for task features requiring a complex integration of sensory information [59].

Recently, Tomassini et al. pointed out different results, showing that the potential to learn a new motor skill is preserved in MS patients across a wide range of disability, as even the most severely damaged patients were capable of performance improvements of similar magnitude to those seen in controls [63].

### **Recent updates-cortical plasticity enhanced by motor and cognitive rehabilitation**

Ibrahim et colleagues studied the impact of rehabilitation (operator-assisted facilitation physiotherapy) on Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity ( $\lambda$  (ax)), radial diffusivity ( $\lambda$  (rad)) of the whole corpus callosum. At the baseline, patients with MS showed significantly lower values in FA and significantly higher values in MD,  $\lambda$  (ax), and  $\lambda$  (rad) compared to control subjects. Differences 2 months after initiating facilitation physiotherapy were in FA, MD, and in  $\lambda$  (rad) significantly higher than differences in healthy controls. In MS patients, FA in the corpus callosum significantly increased while MD and  $\lambda$  (rad) significantly decreased [64].

Very recently, Rasova et al. evaluated the effects of new kind of neurofacilitation approach, motor programme activating therapy (MPAT) with a set of clinical functions and with MRI. Eighteen patients underwent a 1-hour session of MPAT, twice a week for 2 months. A significant improvement in clinical functions, significant increment of fractional anisotropy and significant decrement of mean diffusivity, and decrement of effective connectivity at supplementary motor areas was stated immediately after the therapy. The modifications in clinical functions and diffusion tensor images were also observed one month after the end of rehabilitation [65].

Tomassini et al. stated that the adaptive plasticity of MS patients is modulated by brain systems different than in health subjects. In this latter study, 23 patients with MS and 13 health individuals underwent short-term and long-term training of a visuomotor task. Long term clinical improvement after intervention based on visuomotor task were related to changes in task-related activation in the left superior lobule and right lateral occipital cortex, while health subjects showed changes only in the occipital cortex. Therefore, rehabilitation treatment based on voluntary movements may contribute to enhance functional and structural brain plasticity [66].

In agreement with this assertion, Bonzano et al. pointed out that rehabilitation based on active and voluntary exercises task-oriented, may induce microstructural modifications of white matter bundles involved in voluntary motor control. In this latter study, the effects of a training based on task-oriented motor rehabilitation (active group)

were compared with those of a training based on passive motor exercises (passive group). In active group the bimanual coordination task remained stable, while worsened in passive group. Accordingly in fMRI, passive group, but not active one, showed reduced fractional anisotropy and increased radial diffusivity of corticospinal tracts and corpus callosum [67].

The hypothesis that structural plasticity may be stimulated in brain areas specifically involved in the function with task-oriented rehabilitation is supported by Prosperini et al. [68]. A total of 36 patients affected by MS were subdivided in to two counterbalanced groups: group A underwent 30-minute sessions, 5 days per week for 12 consecutive weeks of home-based video game training (intervention period), followed by a 12-week period without any specific intervention (observation period); group B was treated in reverse order. Patients showed improvement of diffusion tensor imaging measures of superior cerebellar peduncles. Accordingly, there was also a clinical improvement of static balance [68].

### **Cognitive rehabilitation**

Cognitive impairment is rather frequent in persons with MS: it has been reported that almost 40-65% of MS patients could suffer of decreased cognitive abilities. This may determine a profound impact on the patient's social sphere and employability [69].

The cognitive areas involved in MS are quite variegated; patients mainly show a decreased speed in information processing and deficits of executive functions, attention and memory [69].

The term cognitive rehabilitation was perhaps always too narrow, and focused too heavily on remediating or compensating for cognitive impairment. Although some of the fundamental goals of improving and compensating for cognitive abilities continue to be mainstays of rehabilitation efforts, the last 20 years have allowed a richer appreciation for the influence of contextual variables such as the personal, emotional and social impacts of the illness and their interaction with cognitive function. All these factors have been incorporated to an even greater degree into treatment plans and goals.

There are few randomised controlled trials focusing on the effectiveness of neuropsychological intervention in people with MS. In Thomas's et al. Cochrane, 16 studies were identified and included, but no definite conclusions could be made from the review. Two small studies of cognitive behavioural therapy showed significant improvements in depression. To regard the cognitive impairment, three trials highlighted some evidence of effectiveness of cognitive rehabilitation, although this was difficult to interpret because of the large number of outcome measures used [70].

Jonsson et al. led a study on 40 patients with mild to moderate cognitive and behavioural impairment. After short-term treatment, effects on cognitive measures were rather mild, but on the Beck Depression Inventory (BDI) the specific cognitive treatment group reported significantly less depression. After 6 months, only this group showed an improvement on the visuo-spatial memory; the depression rating on BDI were almost maintained [71].

Plohmann et al. evaluated the effects of a specific computer based retraining of four attentional functions on cognitive measures in patients with mild to moderate cognitive dysfunction. Significant improvements of performance for the domains alertness and divided attention as well as an increased performance in an aspect of selective attention were achieved by the respective training programmes. The



increase of performance remained stable for at least nine weeks [72].

Benedict et al. carried out a study on 15 patients with marked cognitive impairment and behaviour disorder. Patients who underwent neuropsychological counselling showed significant positive response on measures of social behaviour (e.g. excessive ego-centric speech) [73].

Mattioli et al. conducted a study on a homogeneous group of Relapsing Remitting (RR) MS patients with low levels of disability and a stable clinical course in the previous year. Patients underwent an intensive (3 hours/week for three consecutive months) cognitive rehabilitation procedure of information processing, attention and executive functions. After rehabilitation, only the treated group significantly improved in tests of attention and information processing, assessed by Paced Auditory Serial Addition Test, and in executive functions, evaluated by the Winsons Card Sorting Test. The authors underlined the usefulness of intensive short duration specific therapy in persons with MS affected by cognitive deficits [74].

The intervention strategies consisted of training of attention determined an increased activation of the cerebral areas that are known to be involved in a network functionally related to attention processing. In a preliminary study, 11 patients with cognitive deterioration were treated with the AIXTENT software to train alertness, divided attention and selective attention. After the rehabilitative training, fMRI images showed an enhanced activation of regions in the cingulated gyrus, precuneus and frontal cortex [75].

Sastre-Garriga et al. observed an increased fMRI activation in right posterior lobe and posterior lobes of cerebellum in 15 patients after a mixed intervention, based on computer-aided training plus game-like group activities. Moreover, patients showed an improved performances in backward version of digit-span. Nevertheless, the authors did not find significant correlation between clinical and fMRI variations, likely because the small size of the sample [76].

More recently, Cerasa et colleagues carried out a double-blind, randomized, controlled trial, in which 13 patients, allocated in cognitive rehabilitation intervention group, underwent a computer-assisted training of several attention ability and information processing tasks, for twice a week, 1-hour sessions for 6 consecutive weeks. After the training, the treated group showed a specific enhanced performances in attention abilities, as assessed by the Stroop task, coupled with enhanced activity in the posterior cerebellar lobule and in the superior parietal lobule [77].

To regard the rehabilitation strategies focused on memory deficits, Chiaravalloti and colleagues studied the effects of a rehabilitative approach called modified Story Memory Technique (mSMT). After intervention, greater activation was evident in the treatment group during performance of a memory task within a widespread cortical network involving frontal, parietal, precuneus and parahippocampal areas, while control group showed no significant changes in cerebral activation. The authors also found a significant correlation between improved memory performances and enhanced activation of the right middle frontal gyrus, which is known to be associated with visual and context-dependent learning [78]. Afterwards, a subset of patients from this latter clinical trial underwent also Resting-State Functionally Connectivity-fMRI, in order to examine the connectivity within the neural networks associated with memory function. In conclusion, the authors hypothesized that cognitive rehabilitation would result in increased integrity of connections within two primary memory

network, the hippocampal memory network and posterior cingulated cortex (default network) [79].

A French-study investigated the effects of cognitive rehabilitation on autobiographical memory. Four patients underwent a training based on the cueing role of mental visual imagery in autobiographical memory. After the rehabilitation, increased activation of posterior cerebral areas specifically involved in memory retrieval (right cuneus, left precuneus, left inferior and superior occipital gyri, left lateral temporal cortex) coupled with significant improvement of autobiographical memory performances were stated [80].

Finally, we report the issues of the studies focused on a wide range of cognitive domains, such as memory, executive functions, attentional processes and information processing speed.

Filippi et al. described the benefits of a 12-weeks training of cognitive rehabilitation in changing the recruitment of several brain areas that are mainly located in the frontal-parietal lobes. Patient underwent intensive computer-assisted cognitive rehabilitation of attention, information processing and executive functions for 12 weeks, performed by the use of a software included in the RehaCom Package with 1-hour session for three-times per week. After training, fMRI demonstrated changes of the activity of the posterior cingulated cortex, precuneus and dorsolateral prefrontal cortex during the execution of the Stroop Test, as well as changes of the activity of the anterior cingulum, posterior cingulated cortex, precuneus left dorsolateral prefrontal cortex and right inferior parietal lobule at rest [51].

Clinically, patients showed an improvement in some tests of attention, information processing and executive functions. Subsequently, the same research group investigated how resting state functional connectivity (FC) of the anterior cingulated cortex correlates with cognitive training. At follow-up, the anterior cingulum showed an increased FC with the right inferior parietal lobule and decreased FC with the right inferior temporal gyrus in the treated group only; some of these FC modifications significantly correlated to enhanced PASAT scores after the training [81].

Bonavita and colleagues studied the effects of short-term computer-based cognitive rehabilitation (cCR) on eighteen patients affected by RRMS, compared with a control group submitted to an aspecific cognitive training. After cCR, patients showed a significant improvement of several cognitive tests exploring information processing speed and verbal and visual sustained memory, as well as a significant increase of the functional connectivity of the default mode network in the posterior cingulated cortex and bilateral inferior parietal cortex. Control group did not show any significant variations on either cognitive performances or functional connectivity.

Very recently, De Giglio and colleagues investigated the effects of an 8-week home-based rehabilitation program by use of the Dr. Kawashima Nintendo Brain Training, an educational video game ended to train memory, attention, visuospatial processing and calculations. After this training, patients showed increased thalamic connectivity in cortical areas that partially overlapped the posterior component of default mode-network. The increased connectivity positively correlated with improvement of cognitive performances (i.e., sustained and divided attention and some aspects of executive functions), suggesting that changes in thalamic functional connectivity induced by cognitive rehabilitation may represent a functional substrate underlying clinical recovery [82].

Rehabilitation setting: It remains unsolved the question regarding

the most suitable rehabilitative setting for PwMS. In this regard, it must be considered not only the efficacy of treatment but also the evidences encompassing the long-term cost-effectiveness.

There are four possible options for the rehabilitative treatment setting in which the patient could be allocated: i) home based therapy, ii) outpatient ambulatory therapy, iii) inpatient hospitalised therapy, iiiii) outpatient hospitalised therapy. Specific guidelines, ended to a rational allocation of PwMS in rehabilitative setting are not available yet. Moreover, there are very few studies comparing the effects of different rehabilitative settings.

Waying back in 1988, a study was conducted to compare the effects of inpatient and outpatient rehabilitation upon functional status. Patients were evaluated using the Incapacity Status Scale and a structured interview. The conclusions of the study showed the effectiveness of inpatient rehabilitation in producing a significant reduction of disability, as compared to outpatient treatment.

More recently, a RCT was performed to investigate the rehabilitation efficacy in terms of functional independence and HRQoL between two different settings. Both inpatient and outpatient settings showed significant improvement in functional independence but only outpatient setting was found to be effective in improving HRQoL [18].

Almost of all of the studies analyse the results of one rehabilitative setting, in comparison with no treated control group (Table 1). Inpatient setting was associated with a significant improvement in functional impairment [83], disability [25] functional independence and HRQoL [27,33]. Trials conducted in outpatient setting demonstrated effectiveness of rehabilitation in improvement of muscular strength [24], walking capacity [32], functional independence [29,33], HRQoL [17,24,26]. Home-based rehabilitation produced significant improvement in HRQoL [37], Balance [68,84] leg estensor power, gait parameters, fatigue.

Below, we report the conclusions of several systematic reviews which searched to assess the effectiveness of multidisciplinary rehabilitation in PwMS to explore rehabilitation approaches in different settings.

Khan et al. [85] reviewed the results of ten trials (9 randomized controlled trials and 1 controlled clinical trial) in 2011, asserting the strong evidence to support inpatient multidisciplinary rehabilitation in producing short-terms gains at the levels of activity (disability) and participation in PwMS. To regard outpatient and home-based rehabilitation programmes, they found a limited evidence for short term improvements in symptoms and disability with high intensity programmes, which translated into improvement in participation and quality of life. For low intensity programmes, there was strong evidence for longer –term gains in quality of life (Khan 2007, reviewed in 2011) [10].

Very recently, Haselkorn et al. [86] reviewed 491 articles appeared from 1970 to 2013 in order to systematically examine the evidence regarding rehabilitation in MS. This review addressed the effectiveness of outpatient or inpatient comprehensive multidisciplinary rehabilitation, as well as of outpatient or inpatient physical therapy to minimized, reduce disability or improve HRQoL in MS. They concluded that comprehensive possibly is effective for improving disability as assessed by Functional Independence Measure (FIM) in patients affected by Primary Progressive MS and Secondary Progressive MS and EDSS 4.0-8.0. Instead, there are inadequate data to support or refute the effectiveness of comprehensive.

## Outcome instruments

Appropriateness of outcome measure in rehabilitation is essential. Some results from rehabilitation in MS could be controversial; it depends on the use of inadequate outcome measures. To bring an example, Romberg et al. found that a long term exercise program determined significant improvement in leg function and ambulation. These changes could be assessed with Multiple Sclerosis Functional Composite (MSFC), whereas no significant effects were seen with the Expanded Disability Status Scale [83]. In a recent meta-analysis for the period 1960-2006, Motl et al. observed a significant effect of aerobic exercise on improving the QoL. These effects were statistically significant when using an MS-specific QoL instrument, whereas there was no significant effect when generic QoL measures were used. The differences may be due to the fact that only MS-specific QoL instruments would be able to capture all peculiar aspects of QoL impacted by the rehabilitation, for a particular patient population such as with MS [87].

Therefore, it plays a crucial importance to set targets achievable with the rehabilitation and even more, to select the most sensitive assessment instruments.

## Conclusion

MS is perhaps the most multifaceted disease among those that cause chronic health disorders. This feature of disease, coupled with the tendency to affect young people over the lifetime more productive, make it difficult to plan the management of disease in both the short and long term, considering that life expectancy is not substantially shortened. Thus, MS is a great challenge which changes the view of life, either for the patient or for his relatives. Rehabilitation management looks at the person with MS any more than the disease. Rehabilitation aims to maximize the functional independence of the person, through the stabilization of functioning, the reduction of disability and the prevention of secondary complications. These objectives can be achieved through an educational process that encourages the functional independence of the individual. Rehabilitation is a process of active change by which a disabled person acquires new skills, needed to optimize his/her physical, psychological and social functions.

Rehabilitation in person with MS has no direct influence on disease progression, studies to date have shown that this type of intervention improves personal activities and ability to participate in social activities, thereby improving quality of life [88].

A lot of reports demonstrate that neurorehabilitation is effective in mitigating disability and improving QoL; it could offer the physician, patients and their caregivers different options of treatment: inpatient, outpatient, home based, etc. on the basis of their desires and preferences, after evaluating family resource and life place. In addition, A detailed assessment of cognitive domains is remarkably important in persons with MS, in order to identify specific deficits and enable a targeted neuropsychological intervention. In this context, the prospect of cognitive rehabilitation offers interesting possibilities, even if further larger randomised studies are needed.

Treatment should be adapted depending on: the individual patient's needs, demands of their surrounding environment, type and degree of disability, and treatment goals. It could be hopeful to have the possibility to select the best way to treat people with MS, taking into account not only medical problems but also social and familiar aspects. In other words, it is necessary to take into account familiar resources, having or not having children, being or not being child of old and ill parents, have the capacity to produce an income, live or not

live in rural or urban areas, have problems with travelling to the centre for rehabilitation, etc. It must be underlined, however, the urgent need for consensus on a core set of outcome instruments to be used in exercise trials and to establish the amount in terms of frequency, cost and effectiveness over a long time period.

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