REVIEW

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# Exercise and Sports Therapy in Multiple Sclerosis

## *Sporttherapie bei Multipler Sklerose*

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## *Summary*

› **Background:** Multiple Sclerosis (MS) is a chronic immune-mediated disease of the central nervous system, accompanied by varying inflammatory manifestations, demyelization and axonal loss. With chronic progressive or relapsing-remitting disease onsets, persons with MS (pwMS) progressively develop impaired functional capacity and show reduced physical activity compared to healthy controls. The role of rehabilitation with exercise as a central component has become an important aspect in the process of reactivating pwMS. The primary aims of rehabilitation are therefore to increase levels of activity and participation leading to increased independence of the participants.

› **Methods:** Compared to other training modalities, endurance training is well studied and has become an efficient strategy in rehabilitation of pwMS, improving fatigue and health-related quality of life. The most common form is usage of a cycle ergometer but aquatic-exercise and yoga have also been studied. The main goal of resistance training is the general improvement of force components using different resistors. An individual-suited resistance training program impacts maximal force, core-stability, arm, leg and trunk muscles of pwMS.

› **Discussion:** Physical activity impacts various growth factors in the central nervous system, primarily via the brain-derived neurotrophic factor (BDNF), the Insulin Growth Factor-1 (IGF-1) and the Vascular Endothel Growth Factor (VEGF). The congnition-promoting effect is achieved via improvement of the metabolic situation in brain tissue, contributing to an increase in brain volume around the Hippocampus. The outstanding cellular adaptation of the BDNF concentrations can be influenced to various degrees by variations in the training protocol.

› **Conclusion:** : Rehabilitation with exercise is a central component in the process of reactivating pwMS . Evidence shows that exercise training in pwMS has the potential to target and improve many components outlined in the ICF model. The reviewed effects of exercise for pwMS have demonstrated improvements in aerobic and functional capacities, fatigue and muscle weakness.

## *Zusammenfassung*

› **Problemstellung:** In den letzten Jahren ist Training und körperliche Aktivität bei Personen mit Multipler Sklerose (PmMS) zu einer zentralen Komponente von rehabilitativen Trainingsprogramme geworden. Das Training stellt dabei einen wichtigen Bestandteil eines zielorientierten multidisziplinären Ansatzes dar, um die funktionellen Einschränkungen zu reduzieren und die Partizipation von PmMS zu erhöhen. Durch das spezifische Training von Ausdauer- und Kraftfähigkeiten können die funktionellen Einschränkungen und der Verlust von motorischen und kognitiven Funktionen reduziert werden. Oft sind die Verluste von Funktionen weniger durch die Diagnose selbst zu begründen, als durch sekundäre Aspekte – wie lange Phasen von chronischer Inaktivität – die den Gesundheitszustand von PmMS weiter einschränken.

› **Methoden:** Regelmäßige körperliche Aktivität wirkt sich auch bei PmMS begünstigend auf die kardiovaskulären Funktionen, die Funktionen der Kraft und die verbesserte Kognition aus. Dabei besteht ein enger Zusammenhang zwischen dem Aktivitätsniveau, den strukturellen Anpassungsvorgängen im Gehirn und der gesteigerten immunologischen Antwort.

› **Diskussion:** Körperliche Aktivität wirkt sich dabei auf verschiedene Wachstumsfaktoren des Zentralnervensystems aus, primär über den Brain-Derived Neurotrophic Factor (BDNF), den Insulin Growth Factor-1 (IGF-1) und den Vascular Endothel Growth Factor (VEGF). Die kognitionsfördernde Wirkung wird über eine Verbesserung der metabolischen Situation des Hirngewebes erreicht, die zu einer Zunahme des Hirnvolumens im Bereich des Hippocampus beiträgt. Die hervorgerufenen zellulären Anpassungen der BDNF-Konzentrationen können durch Variationen der Trainingsprotokolle unterschiedlich stark beeinflusst werden.

› **Ergebnis:** PmMS sollte geraten werden, gewohnte körperliche Aktivitäten aufrecht zu halten oder zu beginnen, da sich ein erhöhter Trainingszustand Einfluss auf die immunlogische Antwort, das Müdigkeitsempfinden und die kardiorespiratorische Belastbarkeit nimmt.

**KEY WORDS:**
Multiple Sclerosis, Exercise, Endurance Training, Resistance Training

**SCHLÜSSELWÖRTER:**
Multiple Sklerose, Körperliche Aktivität, Ausdauertraining, Krafttraining

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## Introduction

Multiple Sclerosis (MS) is a chronic immune-mediated disease of the central nervous system, accompanied by varying inflammatory manifestations, demyelization and axonal loss (12). With chronic progressive or relapsing-remitting disease onsets persons with MS (pwMS) progressively develop impaired functional capacity and show reduced physical activity compared to healthy controls (19). MS predominately affects younger adults where the functional impairments lead to sustained disabilities that directly impact the patient's health-related quality of life (HR-QoL) and their social economic environment (26). The role of rehabilitation with exercise as a central component has become an important aspect in the process of reactivating pwMS. Exercise has become an efficient strategy within rehabilitative programs and is part of a goal-orientated multidisciplinary approach to improve disability and participation in pwMS (4). The primary aims of rehabilitation are therefore to increase levels of activity and participation leading to increase independence of the participants (21).

In general, exercise ranges from passive physiotherapy-based interventions to submaximal endurance training sessions. It has become clear that an eventual worsening of the sensory symptoms – expressed by 40% of pwMS – is temporal and will normalize within half an hour after the exercise session (41). Current recommendations advise pwMS that exercise should be matched with the individual performance capacities (23). Exercise training in pwMS then has the potential to target and improve many components outlined in the ICF model. Over the last decade cytokines and neurotrophic factors recieved increased attention in MS research and addessed the brain-derived neurotrophic factor (BDNF) as an important mediator of neuronal regeneration linking the effects of exercise with MS pathogenesis (2, 38).

Data show connections between elevated neurotrophin concentrations, induction of neuroplasticity and recovery of the motor and cognitive functions (8, 33).

Taken together the beneficial effects of exercise are well studied and the immune-modulating effects of standardized endurance training seem attractive.

## Methods

### Endurance Training

PwMS were long advised not to exercise in order to minimize risk for exacerbations and fatigue (42). Within neuro-rehabilitative programs exercise has become an efficient and important strategy as part of a goal-orientated multidisciplinary approach to improve disability participation and HR-QoL (4). Exercise ranges from passive physiotherapy-based interventions to submaximal endurance training sessions. The most common form is usage of a cycle ergometer, but resistance training (13), aquatic exercise (3, 35) and yoga (30) have also been studied.

The gold standard for the quantification of cardiorespiratory fitness is an individual determination of the fitness level by direct and continuous measurements (breath by breath) of the maximum oxygen consumption ($VO_{2max}$) via ergospirometry (44). $VO_{2max}$ is an important marker for general health and the general exercise performance (15) that is associated with higher physical (walking speed) and cognitive functions (27). When performing Cardiopulmonary exercise test CPET in pwMS the specific clinical symptomology affects mainly the lower limbs and reduces motor efficiency due to accompanying spasticities and motor incoordination limiting the maximum effort of the participants to a subjective felt maximum (32). With disease onsets and progressive loss of muscular functions, exercise performance and compliance to the CPET procedures on cycle ergometers become more difficult and impossible for pwMS with an EDSS>7.0 (40).

Short and exhaustive exercise bouts significantly increase cardiorespiratory fitness in pwMS and lead to up-regulations of T-H2 secretions of BDNF and nerve growth factor (NGF) (20, 43). The achieved beneficial adaptations are associated with the intensity dependent lactate increases during exercise (16). Evidence is evolving that the defective axonal energy metabolism

Table 1

Effects of exercise in pwMS and the resulting interactions on the ICF.

| MS PATHOGENESIS | BODY STRUCTURES | BODY FUNCTIONS | PARTICIPATION |
|---|---|---|---|
| **Inflammatory Processes** | Axonal damage | **Mental:** | **HR-QoL** |
| | | Cognition | |
| | | Fatigue | |
| | | Depression | |
| **Neurodegeneration** | Neuronal Loss | **Cardiovascular:** | **ADL** |
| | | Aerobic Capacity (VO2max) | |
| | | **Musculoskeletal:** | **Leisure** |
| | | Gait | **Work** |
| | | **Sensory** | |
| | | Balance | |

holds a key role in the diffuse axonal degeneration in pwMS. A deficiency in the astrocytic β2-adrenergic receptors may be responsible for a reduced glycogenolysis, resulting in a decreased formation of lactate and glutamine, which are important energy sources for the axons (6). This dose-response relationship between the mode and the chosen exercise intensity, implicates the relevance of the chosen exercise protocols with higher exercise intensities facilitating greater benefits, also in pwMS (11).

### Resistance Training

PwMS show reduced maximal muscle strength measured as isokinetic (7) and isometric (28) muscle contractions compared to healthy controls. Also, the rate of force development is reduced among pwMS (10). This strength impairment seems particular distinct in the lower extremity as compared to the upper extremity (39). The muscle fibre type composition differs in MS patients compared to healthy controls, but the findings are inconsistent. Kent-Braun et al. (19) report a shift in fibre type composition from Type I fibres toward a greater proportion of Type II-a and II-ax fibres resembling the patterns seen in healthy subjects exposed to chronic immobilization.

The main goal of resistance training should be the general improvement of force components using different resistors. Evidence show that an individual-suited resistance training program impacts maximal force, core-stability, arm, leg and trunk muscles of pwMS: ten weeks of resistance training led to an increase of muscle performance leg muscles and core-stability (14), eight weeks training led to 37% increase of maximum voluntary contraction of the leg extensors. However the evaluated training regimes mainly comprise resistance training with moderate intensities and mild progression of the workload. Evidence is evolving that pwMS tolerate higher training intensities, larger training volumes and faster progression achieving larger and faster improvements from this modality (5).

For quantification of the individual training intensity studies distinguish between the overcoming of a one-round maximal resistor and the frequent prevailing against moderate forces. The gold standard for evaluating the individual training workload are isokinetic training machines. Through electronically driven force under constant speed individual muscle groups can be tested but their drawback lies in their complex technical and high financial expenses (13). One should keep in mind that training programs for pwMS should be performed under supervision from experienced personnel, as supervised training programs are superior to non supervised training programs (24).

## Results

### Effects of Exercise on MS Pathogenesis and Disease Progression

Immune responses to exercise generally consist of induced lymphocyte populations (mainly T-cells, B-cells and natural killer cells) in the blood under exercise and immune suppression during regeneration (29). The inflicted damages of the CNS structures lead to dysregulations of the inflammatory balance in favour of a pro-inflammatory state that may be targeted and modulated via exercise (12). MS research has more and more focused on the role of cytokines and neurotrophic factors linking the beneficial effects of exercise found in elder adults and animal studies also with MS pathogenesis. Data from cross-sectional studies in pwMS show positive associations between the levels of cardiorespiratory fitness and measures of grey matter atrophy and white matter integrity: in 21 pwMS (EDSS 1.0-6.0) high levels of cardiorespiratory fitness were positively correlated with grey matter volume and higher focal fractional anisotropy values (33).

However, training interventions studies in pwMS show mixed results: one small study in 15 pwMS (mean EDSS of 2.0) show that inflammatory cytokines IL-6 and the soluble receptor IL-6sR were not altered after four weeks training (30 minutes of cycling at 60% $VO_{2max}$ twice per week) compared with 13 inactive pwMS. Interestingly, the cytokines of the untrained pwMS showed a shift towards a T-H1 profile while cytokine responses of trained pwMS resembled healthy controls (18). In contrast, a RCT with 20 pwMS (EDSS 1.0-4.0) investigating combined endurance (20 min aerobic exercise) and resistance training (20 min strength training) showed a significant decrease of cytokines IFN-γ and IL-17, but not of IL-4 (17). However, training modes and the implicated training intensities are not sufficiently described and may have limited the impact on the database. Another RCT, with 30 pwMS (EDSS between 1.5-6.5) investigated the influences of water immersion involving 3-week supervised training of aquatic-cycling (30 minutes of aquatic-cycling 5 times per week with 65% $VO_{2max}$) – performed on a revolution per minute scaled ergometer mounted in a pool with a water temperature of 28° Celsius – showing significant activation of BDNF regulation compared to 30 pwMS that performed overland cycling (3). The fact that exercise itself does not lead to changes in serum cytokines and neurotrophin concentrations, but that the mode (mild versus strenuous) of the exercise factor plays a more decisive role (31), may be one explanation for this variability.

### Effects of Exercise on Body Functions

**Cardiorespiratory Fitness**

PwMS were for a long time advised not to exercise in order to minimize the risk for exacerbations and fatigue (42). Support for the beneficial effects of exercise training on cardiorespiratory fitness in pwMS has been consistent: A RCT in 60 pwMS (EDSS between 1.5-6.5) comparing 3-week supervised, moderate aquatic- versus overland cycling (30 minutes of aquatic- or overland cycling 5 times per week at 65% $VO_{2max}$) showed significant improvements of cardiorespiratory fitness and exercise performance independent of the cycling mode (3).

Another RCT with crossover in 19 pwMS (mean EDSS of 3.5) compared the effects of moderate endurance training (30 min of leg cycling at 60% $W_{peak}$, 3 days per week over 8 weeks) and neurological rehabilitation (comparable frequency and duration of respiratory – postural and respiratory – motor synergies) on maximal exercise tolerance. Results show significant improvements of $VO_{2peak}$ and $W_{peak}$ in those participants following the endurance training program.

**Cognitive Functions**

Cognitive impairments occur in 43-65 % of pwMS and lead to slowed mental processing speeds and impaired memory (34). Processing speed is the most vulnerable domain followed by working memory and executive functions (22). Findings show that gray matter atrophy is important for the accumulation of cognitive impairments, over time negatively affecting activities, such as ability to work, drive, and participation outcomes e.g. health-related quality of life (HR-QoL) (27).

Only few studies investigated the effects of exercise on cognitive functions:

One RCT examined the effects of three exercise interventions (arm ergometry, rowing, bicycle ergometry or control intervention) in 42 pwMS (EDSS 4.0-6.0) for 8-10 on aerobic fitness and cognitive functions. Cognitive functions were measured with the Symbol Digit Modalities Test (SDMT) and the Verbal Learning Memory Test (VLMT). Significant improvements were seen in aerobic fitness and better performance in aspects of verbal-learning and delayed memory (VLMT), as well as alertness and shift of attention (TAP), but not in working memory (SDMT) or executive functions (RWT and LPS) (5). Another long-termed RCT in 95 pwMS (EDSS 1.0-5.5) combining endurance (preferred mode, cycling or elastic bands) and resistance exercise (10 exercises involving upper and lower extremities with 2 sets and 10-12 repetitions) performed on five days per week over 26 weeks showed no effects on cognition, measured by using the Paced Auditory Serial Addition Task (PASAT) change with exercise training compared with control (36). The beneficial adaptations of exercise on cognitive functions can be associated with induced metabolical situations and cut in energy sources of brain tissue (37).

**Fatigue**

Fatigue occurs in the majority of pwMS and specific therapeutic possibilities are few. Exercise training has the potential to positively affect fatigue in pwMS some studies, however show no effect (1). One long termed RCT in 24 pwMS investigated the effects of aerobic exercise training (40 min of leg ergometry or treadmill walking at light to moderate intensity, 2 days per week under supervision, and self-selected, home-based exercise, 1 day per week) on fatigue (Modified Fatigue Impact Scale, MFIS) and quality of life. Aerobic exercise was compared versus a control condition (monthly visit with physiotherapist) and led to significant reductions of fatigue scores that was maintained for over 12 weeks after the intervention, whereas no change was observed in the control group (25).

It has to be considered that fatigue questionnaires only assess subjective feelings of the patients related towards fatigue and pwMS may tend to give higher scores, as they feel subjectively more fatigued but still may be able to tolerate moderate exercise intensities.

### Effects of Exercise on Activation and Participation

In pwMS HR-QoL is often impaired and reflects status of reduced functional disability, mental complications and altered social behavior (26). The primary aim of standardized rehabilitation in pwMS is to improve levels of activation and participation of pwMS using the International Classification of Functioning Disability and Health (ICF, (4, 21)). In pwMS the impacts of training on HR-QoL show mixed results: A long-termed RCT in 95 pwMS (EDSS 1.0-5.5) that combined endurance (preferred mode, cycling or elastic bands) and resistance exercise (10 exercises involving upper and lower extremities with 2 sets and 10-12 repetitions) performed on five days per week over 26 weeks showed no effects on HR-QoL after three months of training (36). In contrast another RCT in 31 pwMS (EDSS 3.5-5.5) showed significant effect for the physical component score of the SF-36 for the group performing 24 weeks (12 weeks training, 12 weeks follow-up) progressive resistance training (twice per week, 5 exercises for the lower extremities: 3-4 series with 8-15 repetitions) (13). Studies evaluating the effects of standardized endurance and resistance training in pwMS for HR-QoL measures are mainly performed overland but several water-training studies in pwMS also show improvements in HR-QoL:

One small pilot study in 19 pwMS showed significant improvements of HR-QoL in better social functioning after 12 weeks of aquatic training performed for 1 hour twice per week (35). Another larger scaled RCT in 73 pwMS showed that after 20 weeks of Ai-Chi under immersion significantly affected pain and spasticity (9). However most water-training studies performed with pwMS hold methodological weaknesses as they show low power and are poorly controlled, as immersion depth and training intensities are not specified.

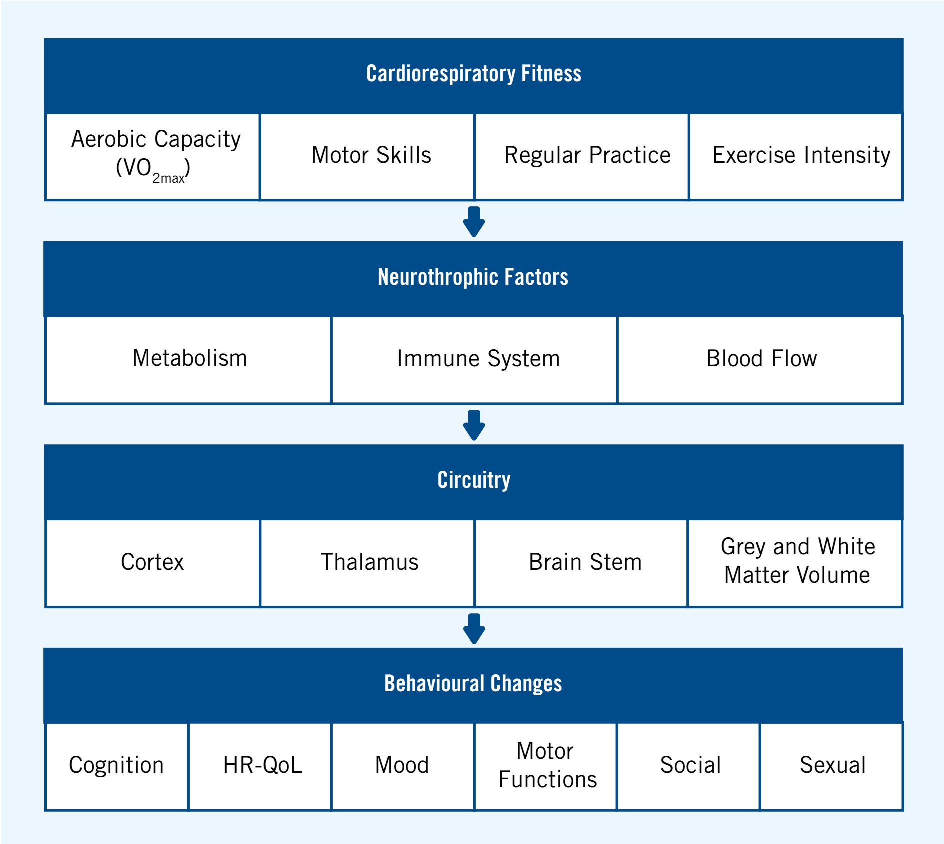


Figure 1

Cardiorespiratory fitness and enhanced plasticity in multiple sclerosis.

## Conclusion

The role of rehabilitation with exercise as a central component is important in the process of reactivating pwMS. Evidence shows that exercise training in pwMS has the potential to target and improve many components outlined in the ICF model. The reviewed effects of exercise for pwMS have demonstrated improvements of aerobic and functional capacities, fatigue and muscle weakness. It remains an open question whether exercise reverses impairments caused by the disease itself or only reverses the effects of long phases of chronic inactivation adopted by many pwMS.

Future research must clarify the specific training intensities of exercise that is needed to further specify the impacts of the exercise programs in pwMS. This implicates a precise definition of the duration, frequency and intensity of exercise performed in rehabilitative settings. Also, only few studies investigated the feasibility of endurance or resistance training in severely disabled (EDSS 7.0-8.0). Data of a pilot study (40) are promising as they show that training performed at sufficient intensities is tolerated and cardiovascular adaptations are achieved in this specific patient group.

**Conflict of Interest**

*The authors have no conflict of interest.*

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