Effects of exercise on fitness and cognition in progressive MS: a randomized, controlled pilot trial

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Abstract

Background: Exercise may have beneficial effects on both well-being and walking ability in multiple sclerosis (MS). Exercise is shown to be neuroprotective in rodents and may also enhance cognitive function in humans. It may, therefore, be particularly useful for MS patients with pronounced neurodegeneration.

Objective: To investigate the potential of standardized exercise as a therapeutic intervention for progressive MS, in a randomized-controlled pilot trial.

Methods: Patients with progressive MS and moderate disability (Expanded Disability Status Scale (EDSS) of 4–6) were randomized to one of three exercise interventions (arm ergometry, rowing, bicycle ergometry) for 8–10 weeks or a waitlist control group. We analyzed the drop-out rate as a measure of feasibility. The primary endpoint of the study was aerobic fitness. Secondary endpoints were walking ability, cognitive function as measured by a neuropsychological test battery, depression and fatigue.

Results: A total of 42 patients completed the trial (10.6% drop-out rate). Significant improvements were seen in aerobic fitness. In addition, exercise improved walking ability, depressive symptoms, fatigue and several domains of cognitive function.

Conclusion: This study indicated that aerobic training is feasible and could be beneficial for patients with progressive MS. Larger exercise studies are needed to confirm the effect on cognition.

Trial Registration: ISRCTN (trial number 76467492) <http://isrctn.org>

Keywords

Aerobic exercise, clinical trial, cognition, depression, fatigue, fitness, motor function, multiple sclerosis, progressive multiple sclerosis, rehabilitation, walking ability

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Introduction

Currently approved disease-modifying therapies (DMTs) for multiple sclerosis (MS) have limited impact on the neurodegenerative component of the disease. Therapeutic effects on cognition, which might be the best clinical correlate of widespread neurodegeneration, are modest at best.^{1,2} One review shows that attempts to develop pharmacological therapies for cognitive impairment have been unsuccessful in MS.³ Evidence for the effectiveness of rehabilitation strategies to ameliorate cognitive deficits in MS is limited, as well.⁴ Therefore, therapeutic approaches that target neuroprotective mechanisms and may improve cognition and motor function are urgently needed.⁵

Intriguingly, exercise is shown to promote neuroregeneration and plasticity and to improve learning and memory, in rodents.⁶ Several randomized controlled trials (RCTs) of

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aerobic exercise in both young healthy and aging adults demonstrate improved cognitive function.⁷ Exercise may therefore have therapeutic potential for improving cognitive function in MS, but empirical evidence from randomized controlled trials is lacking.⁸

Since the first RCT of exercise in MS by Petajan et al.⁹, both improved quality of life and walking ability in MS after exercise training were confirmed by several RCTs.¹⁰ ¹¹ In addition to improving well-being, recent experimental evidence suggests that exercise might directly affect pathology, by showing neuronal protection during experimental autoimmune encephalomyelitis (EAE).¹²

Exercise therapy might be a particularly useful approach for MS patients with progressive disease, as treatment options are very limited.¹³ On the other hand, the more advanced motor impairment in secondary progressive MS (SPMS) might interfere with the ability of the patients to perform aerobic exercise training programs. Therefore, there is a need to rigorously test the feasibility and effectiveness of exercise in progressive MS.

In the present pilot-RCT, we aimed to compare three endurance-training interventions in progressive MS patients. We expected exercise to improve their physical fitness, walking ability and cognitive function. Based on a meta-analysis in non-MS populations⁷, we expected improved performance in learning/memory, attention and executive function.

Materials and methods

Study design, overview and patient recruitment

Our study was a RCT of three different exercise training tools (arm ergometry, rowing and bicycle ergometry) and a waitlist control group with progressive MS patients with moderate disability (see Supplemental Figure). The training programs consisted of 8–10 weeks of standardized exercise with 2–3 sessions per week. This time frame was chosen as a pragmatic approach, to also allow short interruptions of the training with the aim of obtaining about 20 training sessions. The training program was tailored to the individual level of fitness of the participants, as determined by standard ergometry at baseline. The feasibility measure of the study was the percentage of subjects completing the trial.

Our main hypothesis was that the training program would increase fitness, as measured by increased peak oxygen consumption (VO_2), and would improve walking ability, as measured by gait tests. The primary endpoint was aerobic fitness (as defined by peak oxygen consumption during an exhaustion test). Secondary endpoints were: walking ability (as defined by the 6-Minute Walk Test (6MWT)), cognitive function (as measured by a neuropsychological battery), depressive symptoms and fatigue. All endpoints were assessed at baseline, as well as at the end of the 8–10 week intervention (unblinded to the group). Patients were recruited through the MS outpatient clinic at

the University Medical Center Hamburg Eppendorf, as well as through advertisements on the website of the German MS Society and leaflets left in neurologists' offices. We also contacted patients from our database who had agreed to be informed about new studies.

Standard protocol approvals and patient consent

The trial was approved by the ethics committee of the Chamber of Physicians, City of Hamburg, Germany (Registration Number PV3689). Participants provided written informed consent prior to enrollment.

Participant inclusion and exclusion criteria

Patients had to meet diagnostic criteria for clinically definite MS¹⁴ with a secondary-progressive disease course¹⁵ and moderate disability (EDSS 4–6). To enhance recruitment, we later also allowed patients with primary-progressive MS (PPMS) to enter the trial, as long as they met the EDSS inclusion criterion.

Patients were excluded if they had any medical contraindications for exercise therapy (cardiovascular or major orthopedic disease, general medical contraindications for increased aerobic activity) as assessed by self-report using the revised Physical Activity Readiness Questionnaire (rPAR-Q).¹⁶ We excluded patients if they had started immunomodulatory therapy within the last 6 months, undergone steroid therapy within the last 4 weeks, documented relapses within the last 12 months, abnormal liver or kidney function, immunodeficiency, diagnosis of other serious medical illnesses, or if they had severe developmental, psychiatric and neurological disorders other than MS. Eligibility was determined by an experienced senior neurologist. As no previous studies were available to power the exercise trial, its sample size was based on patient availability, with a recruitment goal of $n = 40$ (at least $n = 10$ in each group).

Randomization

Patients were consecutively randomized to one of the four groups, using an automated biased coin algorithm.¹⁷ This approach used the a priori defined variables age, sex, EDSS and previous group size. To ensure a concealed allocation, we performed randomization after determining eligibility.

Individually-tailored training intervention

The training schedule for each participant was tailored to the individual results from a bicycle ergometry performance test that assessed aerobic fitness levels.¹⁸ Since MS patients might not be able to reach their maximum performance in a stepwise exhaustion test, we used a submaximal performance index (aerobic threshold (AT)) for the adjustment of the training intervention.

The training was then performed with the modalities the participants were randomized to. We used the following equipment for training: First Degree Fitness® E-920 Upper Body arm ergometer, the Ergofit® 3000 bicycle ergometer and the Waterrower®.

We determined the training levels using a performance test (ramp test) on the specific selected training tool (see Supplemental Figure). We used the performance in Watts (W) recorded at the individual AT as an anchor for the following training intensity categories: AT, 120% of AT and 130% of AT. The length of each training interval and the target performance were steadily increased with every training session (including regeneration sessions), according to a predefined training plan. The performance as well as subjective work load ratings (Borg scale) were recorded during each training session.¹⁹ The length of the training sessions steadily increased from 15 to 45 minutes (see Supplemental Table 1). All training sessions were performed at the Department of Physiotherapy, University Medical Center Hamburg-Eppendorf, under the supervision of a licensed physiotherapist.

Outcome measures

Aerobic fitness. Participants started cycling at 25 W and resistance was steadily increased with an incline of 12.5 W/min. We obtained VO_2 and heart rate continuously and recorded maximum power. We measured lactate every 2 minutes. As some patients ($n = 14$) were unable to perform this standard ergometry, for these participants, an easier protocol was used starting at 8W with incremental increases of 8W/min. These tests were conducted at the Competence Center for Sports and Exercise Medicine in Hamburg, Germany by an experienced sports scientist.

Motor function. We assessed walking ability before and after the training program, using the 6MWT.²⁰

Neuropsychological function. Cognitive impairment in MS affects domains including attention, processing speed, long-term memory and executive function.²¹ Therefore, we administered a battery of standardized neuropsychological tests that covered these domains.

The “Symbol Digit Modalities Test” (SDMT)²² was utilized to measure processing speed. The “Verbal Learning and Memory Test” (VLMT) was used to evaluate declarative memory and learning abilities.²³ Here, a word list of 15 unrelated words is presented 5 times. The test provides a measure of learning (sum of correctly recalled words during the 5 trials), plus delayed recall after 30 minutes. To assess attention, we used the “alertness” and “shift of attention” subtests of the computerized “Test Battery of Attention” (TAP).²⁴ The “alertness” TAP subtest consists of a simple reaction time test, with and without cue (for “tonic alertness” and “phasic alertness”, respectively). In the TAP subtest “shift of attention”, a

Posner paradigm with valid and invalid cues is used: After valid cues, the stimulus is presented in the area, as indicated by the arrow. After invalid cues, the stimulus is presented on the side opposite to that indicated by the arrow. We quantified executive function with subtest 3 of the “Achievement Testing System” (Leistungsprüfsystem (LPS)).²⁵ In this test, subjects select a symbol that does not fit a sequence, i.e. they identify the rule behind the sequence. The LPS was employed as a measure of logical reasoning. In addition, we assessed verbal fluency using the “Regensburg Verbal Fluency Test” (RWT), specifically subtest “letters G-R”.²⁶ In a previous study, we demonstrated that the VLMT, RWT and TAP are sensitive for detecting cognitive impairment in MS.²⁷

Patient-based outcome measures. We assessed depression using the self-reported version of the 30-item “Inventory of Depressive Symptoms” (IDS-SR₃₀).²⁸ We measured fatigue with the “Modified Fatigue Impact Scale” (MFIS).²⁹

Statistical analyses

We tested the feasibility of the different exercise modalities by analyses of drop-out rates, using Fisher’s exact test. Based on visual inspection of Quantile-Quantile (Q-Q) plots, we conducted statistical analyses using parametric tests. According to guidelines for statistical analysis of clinical trials, published by The European Agency for the Evaluation of Medicinal Products (CPMP/ICH/363/96 and CPMP/EWP/2863/99), we computed the primary statistical analysis for all outcomes using ANCOVA (Analysis of covariance) models adjusting for baseline measurement of the respective outcome variable, to evaluate treatment effects (measured as change from baseline). No other covariates were included in this primary analysis. As recommended, this model also did not include treatment by covariate interactions. In the case of significant F values in the ANCOVA model, we conducted planned pairwise comparisons for each intervention group (bicycle, arm ergometry and rowing) compared to the waitlist control group.

A total of 14 ANCOVAs were computed: One for the primary endpoint (VO_2 peak), and one for each of the secondary endpoints walking ability (6MWT), depressive symptoms (IDS) and fatigue (MFIS) - for the multidimensional assessment of cognitive function, we computed 10 ANCOVAs, of which four assessed attention. In accordance with European Medicines Agency (EMA) guidelines, we also computed sensitivity analyses using ANCOVA models, adjusting for baseline as well as sex, age, EDSS and patient MS type (SPMS or PPMS), in addition to the primary analysis. For the ANCOVA models, we used available data from all our subjects who completed the pre- and post-intervention assessments ($n = 42$).

Finally, we also computed non-parametric intention-to-treat (ITT) analyses, using Kruskal-Wallis tests

Figure 1. Participant flow chart.

where the patients who dropped out were assigned the lowest rank. In the results section, we report p values from the primary analysis (ANCOVA, adjusted for baseline). The p values from sensitivity analyses can be found in Supplemental Table 2. Pre- and post mean scores, standard deviations as well as confidence intervals are indicated in Supplemental Table 3 and Spearman correlation coefficients of change scores are indicated in Supplemental Table 4. We performed statistical analyses and conducted 2-tailed testing, using the statistics package R 2.15.2.³⁰ A value of $p < .05$ was considered statistically significant.

Results

Patient sample

We sent out 423 letters advertising the study. Patients who indicated interest in participating ($n = 80$) were contacted by phone for further screening. We examined 50 MS patients in person at the MS clinic. After screening, 47 patients met our inclusion criteria and were randomized to one of the four treatment arms: arm ergometry, rowing, bicycle ergometry, waitlist control (see flow chart in Figure 1 and Table 1).

Feasibility

As a measure of feasibility, we analyzed MS patient drop-out rates in the four groups. Of the 47 study participants, 42 finished the trial, while five dropped out. The drop-out rate did not differ between the groups ($p = .892$; Table 1), indicating that exercise intervention is feasible in progressive MS with moderate disability (EDSS 4–6). Reasons for not completing the trial included logistic and mobility difficulties ($n = 3$), fatigue ($n = 1$) and injury unrelated to the study ($n = 1$). Baseline characteristics for the four groups are shown in Table 1. On average, the subjects exercised 22 sessions. The average Borg rating during the sessions was 4.6.

Effects of exercise on fitness

Exercise induced significant improvements in aerobic fitness, as measured by VO_2 peak during the bicycle ergometry test (Figure 2, $p = .029$). Only the bicycle ergometry group differed significantly from the control group ($p = .003$).

Effects of exercise on motor function

Exercise significantly improved distance walked by patients during the 6MWT (Figure 3; $p = .012$). Significant

Table 1. Clinical baseline characteristics and training intensity.

	Arm	Rowing	Bicycle	Control
Drop-outs (n, %)	2 (16.6%)	1 (8.3%)	1 (8.3%)	1 (10%)
Subjects completing	10	11	11	10
Age (years)	49.1±8.5	50.9±9.2	48.8±6.8	50.4±7.6
Sex (m/f)	5/5	4/7	5/6	4/6
Education (years)	13.7±2.7	12.8±3.7	13.2±3.3	12.9±3.7
Disease duration (years)	17.1±7.2	14.1±6.1	13.3±5.4	18.9±9.8
EDSS (score)	5.2±0.9	4.7±0.8	5.0±0.8	4.9±0.9
MS type (SPMS/PPMS)	8/2	7/4	8/3	8/2
Number of sessions	21.1±0.5	21.7±0.4	22.6±0.9	N/A
Average Borg rating	4.3±0.5	5.3±0.3	4.3±0.1	N/A

EDSS: Expanded Disability Status Scale, SPMS: secondary progressive multiple sclerosis, PPMS: primary progressive multiple sclerosis. Data given as mean±standard deviation.

Figure 2. Effects of standardized exercise therapy on aerobic fitness of MS patients. A significant training effect was observed in VO_2 peak consumption during the step-wise bicycle ergometry exhaustion test, the primary endpoint of the study. Each dot represents one patient. Asterisks indicate significant pairwise comparisons (* < .05; ** < .01). ml: milliliter; min: minutes; MS: multiple sclerosis; VO_2 peak: peak oxygen consumption.

improvements were seen for both the arm ergometry ($p = .003$) and bicycle ergometry groups ($p = .005$), in comparison to the control group.

Effects of exercise on neuropsychological function

Exercise improved 4 out of 10 neuropsychological measures. Exercise significantly improved verbal learning, as measured by the VLMT ($p = .011$, Figure

Figure 3. Effects of standardized exercise therapy on walking ability in MS patients. Exercise therapy significantly improved walking ability, as measured by the 6MWT. Each dot represents one patient. Asterisks indicate significant pairwise comparisons (* < .05; ** < .01). ergo: ergometry; MS: multiple sclerosis; 6MWT: 6-Minute Walking Test.

4(a)). Improvements were significant for the arm ergometry ($p = .007$), the rowing group ($p = .001$) and the bicycle group ($p = .009$), as compared to the waitlist control group. In addition, a significant effect was found for VLMT delayed recall ($p = .002$, Figure 4(b)). Again, all exercise groups showed significant improvement, when compared to the waitlist control group (arm ergometry $p = .004$; rowing $p < .001$; bicycle ergometry $p < .001$).

Figure 4. Effects of standardized exercise therapy on neuropsychological function. (a) Exercise resulted in significantly more words remembered in the learning trials 1–5 of the VLMT. (b) Moreover, significant differences in delayed recall trial 7 were seen. (c) Exercise significantly improved mean reaction times in the TAP alertness and (d) TAP shift of attention subtests. Each dot represents one patient. Asterisks indicate significant pairwise comparisons (* < .05; ** < .01). TAP: Test Battery of Attention; VLMT: Verbal Learning of Memory Test.

Significant group differences were observed for the TAP subtest “tonic alertness” ($p < .001$; Figure 4(c)). The bicycle ergometry group showed significant improvements, compared to waitlist controls ($p = .005$). Furthermore, we saw significant effects in the TAP subtest “shift of attention” (valid cue $p = .007$; Figure 4(d)). Again, the arm ergometry ($p = .026$), as well as the bicycle ergometry group ($p = .002$), showed significant improvements, compared to waitlist controls. No effects

of exercise were seen for the two other TAP subtests, RWT, LPS and SDMT.

Effects of exercise on mood and fatigue

At baseline, 23 patients (49%) had IDS scores of 18 or higher (indicating moderate to severe clinical depression). Moreover, 27 patients (64%) had a MFIS score of 38 or higher at baseline, indicative for substantial fatigue. Exercise

significantly decreased depressive symptoms as per IDS ($p < .001$), with arm ergometry ($p = .001$) and bicycle ergometry ($p = .035$) showing significant improvements, compared to the waitlist control group. Finally, exercise also significantly improved fatigue, as per MFIS total score ($p = .019$), but only the arm ergometry group was significantly better than waitlist control ($p = .013$).

Associations between physical fitness, walking ability and cognition

We saw significant, albeit small-to-moderate correlations between improvements in the VO_2 peak and the VLMT, as well as walking ability (as measured by the 6MWT) and measures of attention, fatigue and depression (Supplementary Table 4).

Discussion

In this study, we obtained the first evidence for beneficial effects of exercise on physical measures (aerobic fitness and walking ability), as well as neuropsychiatric symptoms (cognitive impairment, depressive symptoms and fatigue) in progressive MS.

In MS, exercise studies mostly focused on endpoints, such as walking ability¹⁰ and quality of life¹¹. Given the high prevalence of neuropsychiatric symptoms such as depression, fatigue and cognitive impairment in MS³¹, our preliminary results obtained in this pilot study indicate that exercise might have therapeutic potential for these important symptom domains. Despite the evidence for the beneficial effects of exercise on brain function provided by animal models and RCTs in older healthy adults, only one study to date explored the effects of exercise on cognitive function in MS.³² This trial used a 6 months training intervention with aerobic exercise at a low intensity (2–3 on the Borg scale), with one class per week plus home exercise, and found no significant effects on neuropsychological tests, compared to yoga delivered at the same frequency. In contrast, herein we report significant improvements in learning, memory and attention after exercise training at a higher intensity (mean Borg scaling 4.6). Furthermore, for most of our endpoints, namely VO_2 peak, depression, fatigue and measures of attention, the strongest effects were seen in the bicycle group. Therefore, further studies are needed to determine optimal exercise intensity, as well as to verify the most effective training modalities required to gain beneficial effects on neuropsychiatric symptoms in MS.

Importantly, we found 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 function (RWT and LPS). Memory and attention were also shown to be consistently improved by exercise training in a recent meta-analysis of RCTs in healthy aging adults.⁷ On the other hand, this meta-

analysis also reported beneficial effects on executive function and processing speed, which we did not find in our sample. Whether this is due to chance, limited statistical power in our study or whether there might be domain-specific differences in the effects of exercise, depending on the patient population and exercise conditions, remains to be elucidated.

Higher levels of fitness in MS patients are found to be correlated cross-sectionally with higher structural connectivity³³ and higher gray matter density³⁴, using neuroimaging. Together, these data suggested that physical fitness may be related to less severe CNS damage and higher structural integrity of brain networks that are important for cognitive function, such as learning and memory in MS.

Our study suggested that exercise may improve walking ability in progressive MS. This corroborates and expands the evidence from one recent uncontrolled trial resulting in increased walking ability after 8 weeks of mixed aerobic, resistance, and balance training in progressive patients with EDSS 4–6.³⁵ Intriguingly, we found improved walking ability, not only in the bicycle ergometry group, but also for the arm ergometry training. The underlying mechanisms for improved walking ability after upper limb training in MS are unclear and warrant further investigation. One possibility is that the increased walking ability may be due to contributions of improved cardiorespiratory function toward walking, as was previously shown for patients with peripheral arterial disease^{36, 37}; however, since in our study the arm ergometry group did not show significant improvement in the VO_2 peak, this explanation seems less likely. Another possibility is that better core stability, through the training of abdominal and back muscles by arm ergometry, could help to stabilize the body during movement, thereby improve walking ability. Alternatively, improved walking ability could be a non-specific result of the frequent trips to the training facility, which may have provided some walking training, but the rowing group had the same frequency of trips without these significant improvements. This should be investigated in future studies.

Some other limitations of our study need to be considered: First, the study sample was small and the findings, particularly on cognitive function, require replication in larger samples. The significant increase in fitness might have, at least in part, been due to the decreased VO_2 peak in the control group; however, other outcomes remained stable (6MWT) or slightly improved in controls (VLMT). Therefore, we believe that the intervention effects are not in general based on a worsening of the control group.

Secondly, our control condition consisted of a waitlist group, rather than a non-exercise control condition delivered at the same frequency. Therefore, we cannot entirely rule out that some of the effects, particularly those seen in patient self-reporting measures such as the IDS and MFIS, may be contributed by non-specific factors, such as attention from the therapist or social support from other

patients. However, the three different intervention groups received the same frequency of visits, yet they did not show the same pattern of therapeutic effects in the objective tests of aerobic fitness, walking ability and neuropsychological function. This makes such non-specific effects unlikely to explain our findings.

A related limitation might be that we had multiple secondary endpoints, particularly in the neuropsychological domain. This was because of the lack of previous data regarding the question which MS-related cognitive impairments might be most likely to be affected by exercise.

Our study should therefore be considered a pilot trial; however, the consistent pattern of improvements across endpoints (with strongest improvements always in the bicycle group) would argue against a chance finding based on multiple testing.

While the short-term effects of our exercise training study are encouraging, it remains unknown whether these effects can be sustained over longer periods of time. Maintenance of exercise in MS remains a major issue³⁸ and a better understanding of the barriers involved, as well as development of effective strategies to overcome these, are needed.³⁹ Moreover, our findings were obtained in a sample of progressive MS patients with moderate disability (EDSS 4–6). It therefore remains to be seen if our results can be extended to higher disability ranges.

In summary, this trial provided the first evidence for beneficial effects of standardized exercise training on aerobic fitness, walking ability, cognitive function and neuropsychiatric symptoms in patients with progressive MS and moderate-to-advanced disability. Given the limited pharmacological treatment options for progressive MS, further investigation of exercise interventions in progressive MS is clearly warranted.

Conflict of interest

The authors declare that there are no conflicts of interest.

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