Sport Sciences for Health (2019) 15:559–567
https://doi.org/10.1007/s11332-019-00545-1

ORIGINAL ARTICLE

High-intensity interval ergometer training improves aerobic capacity and fatigue in patients with multiple sclerosis

Marc Wonneberger[1] · **Stephan Schmidt**[2,3]

Received: 27 December 2018 / Accepted: 6 March 2019 / Published online: 29 March 2019

Abstract

Background Moderate endurance training leads to a significant improvement of aerobic fitness and fatigue in patients with multiple sclerosis (MS). However, the effects of high-intensity interval training (HIIT) have not systematically investigated.
Aim To determine the effects of short-term HIIT on aerobic fitness and fatigue in MS patients.
Design Prospective monocentric, randomized, simple blinded cohort study.
Settings Participants exercised for 8 weeks on a bicycle ergometer three times weekly for 8 weeks.
Population Forty patients with relapsing–remitting MS and an extended disability status score (EDSS) of <3.5 participated.
Methods For 8 weeks, participants exercised three times weekly for 30 min according to two different protocols (HIIT versus moderate endurance training). Measurements were taken at baseline and after 8 weeks of training. Individual aerobic fitness (VO_{2peak}) was assessed via a stepwise ramp protocol, fatigue by the Fatigue Severity Scale (FSS), and ambulation was measured by the Timed 25-Foot Walk Test (T25-FW). Data were analysed according to the intention-to-treat (ITT) approach.
Results Aerobic fitness increased significantly in the HIIT group (pre: 26.7 ± 6.1, post: 29.7 ± 6.6 ml/min/kg; $p < 0.04$). No changes with regard to FSS and T25FW were detected in both groups. However, sub-group analysis revealed a significant decrease of fatigue in patients with elevated baseline fatigue (pre: 5.00 ± 0.7, post: 4.7 ± 1.2; $p = 0.03$).
Conclusions HIIT is a promising time-efficient approach in subjects with MS leading to rapid improvement of aerobic fitness.

Abbreviations

HIIT	High-intensity interval training
MS	Multiple sclerosis
EDSS	Extended disability status score
FSS	Fatigue Severity Scale
T25-FW	Timed 25-foot walk Test
ITT	Intention-to-treat
VO_2max	Maximum aerobic capacity
MT	Moderate training

Introduction

Multiple sclerosis (MS) often leads to impaired physical activity and the associated negative health consequences. Even in the early stages of the disease, physical activity is reduced as compared to the healthy population [1, 2]. One of the most frequent symptoms of MS is fatigue, which has a significant impact on day-to-day activity and at a higher degree of severity may bring in its wake significant socio-economic consequences [3, 4].

Numerous studies have shown that physical activity has a positive effect on a variety of attendant symptoms associated with MS [5–10]. Moderate endurance training is considered to be safe and easy. However, a significant time commitment is necessary to achieve the desired results on a physiological or subjective basis [11]. The same training regime in terms of duration and frequency results in a distinct improvement of aerobic fitness, i.e., peak aerobic capacity (VO_{2peak}), in healthy individuals [12–14].

The effects of "high-intensity interval training" (HIIT) on the cardiovascular system have recently been reviewed [15]. However, there are as yet limited insights to what extent improvement of peak aerobic capacity (VO_{2peak}) may affect

✉ Stephan Schmidt
schmidt@neurologie-in-bonn.de

[1] Schule für Physiotherapie Gummersbach-DAA Gesundheit und Soziales, Becketalstraße 1-3, 51643 Gummersbach, Germany

[2] Neurologische Gemeinschaftspraxis Bonn, Gesundheitszentrum St. Johannes, Kölnstr. 54, 53111 Bonn, Germany

[3] Department of Neurology, Ruhr-University of Bochum, Knappschafts-Krankenhaus Langendreer, An der Schornau 23-25, 44892 Bochum, Germany

MS-specific symptoms such as fatigue [15–17]. By contrast, positive effects of HIIT have been demonstrated in patients with other chronic conditions such as coronary artery disease and even in cancer patients with fatigue [18, 19].

We have previously shown that moderate, ambulation-based endurance training leads to a significant improvement of aerobic fitness and fatigue after 9 months in patients with fatigue [11]. Based on these results, the present study aims to investigate, if HIIT might result in a comparable reduction of fatigue in patients with MS in a shorter period of time due to the more rapid improvement of physiological capacities. In contrast to our previous study, the exercise program was performed on a stationary ergometer to allow for standardized exercise conditions.

Patients and methods

Ethics

The study was approved by the Ethics Committee of Deutsche Sporthochschule, Cologne, Germany. All participants gave informed consent prior to study participation.

Subjects

Forty participants (31 females/9 males) were recruited from the MS outpatient center "Neurologische Gemeinschaftspraxis Bonn" meeting the following inclusion criteria: (1) a confirmed diagnosis of relapsing–remitting MS (RR-MS) according to the revised McDonalds criteria [20]; (2) Expanded Disability Status Scale (EDSS) of ≤ 3.5; (3) age between 18 and 55 years. Patients with secondary or primary progressive MS, a temperature sensitive form of MS, and a previous history of heart or pulmonary disease as well as arterial hypertension were excluded. Pregnancy was also an exclusion criterion. The trial duration was 8 weeks with a baseline and exit examination. Patients were randomly assigned to one of the two intervention groups.

Neurological examination

A neurological examination was performed by an experienced neurologist to determine the EDSS at baseline.

Ramp test (VO_{2peak} test)

The primary endpoint was the change in VO_{2peak}, which was determined according to the established ramp protocols [21]. Testing was performed using a cycle ergometer (Schoberer Rad Messtechnik GmbH - SRM GmbH). After a warm-up of 6 min at an intensity of 1 W/kg, the intensity was gradually increased by 8 watts every 10 s. This particular approach was derived from ergometer exercise protocols in cardiology in order to achieve exercise intensities above the 1 W/kg threshold [22] by pre-activation of the aerobic system [21, 23]. The exercise test was discontinued at a respiratory exchange ratio (RER) exceeding 1.1. Further termination criteria were defined as any mention of unease or worsening of pre-existing neurological symptoms, respiratory distress, lack of an adequate elevation, or disproportionate elevation of heart rate beyond the known maximum heart rate and muscle pain. Patients were continuously encouraged throughout the entire test.

VO_2 was measured by breath-by-breath analysis using the open-circuit spirometry system ZAN 600 USB (nSpire Health GmbH, Germany). O_2 consumption and CO_2 expiration were measured continuously. The highest value was defined as VO_2 peak expressed as ml O_2/min/kg with regard to the body weight. The details have been described elsewhere [11].

During the ramp test, the work rate was continuously monitored using an ergometer with an integrated measurement system (SRM Science PowerMeter). Peak power was defined as the wattage at which a plateau of VO_2 was reached despite a continued increase in work rate. The individual peak power was used to determine exercise intensity in each participant.

Fatigue and walking speed

There were two secondary endpoints: (1) fatigue as measured by the Fatigue Severity Scale (FSS) [24] which has been shown to be suitable to detect changes in fatigue over time [25]; (2) changes in walking speed as assessed by the Timed 25-Foot Walk Test (T25-FW) which measures gait velocity [26]. Improvement of gait velocity by more than 20% is generally considered clinically significant [27].

According to the FSS, sub-groups for further analysis were based on a cut-off of 4.0 [< 4.0 = non-fatigue group (nFG) versus ≥ 4.0 = fatigue group (FG)] [28, 29].

Exercise program

The trial was conducted as a prospective, monocentric, randomized, unblinded cohort study, in a pre-/post-design. There was no control group. The individual training intensity was derived from the peak power output during the ramp test. Group I exercised constantly at 50% of peak power output (moderate training = MT group), while Group II performed intensive intervals: 7.5 min warm-up at 40–50% of peak power output plus eight integrated 60 s intervals at an intensity of 70% of the peak power output in alteration with 60 s at an intensity of 50% of the peak power output plus 7.5 min cool down at 40–50% of peak power output (HIIT group). Exercise sessions were

performed on a stationary bicycle ergometer in a fitness centre close to the patients' residence, three times weekly for 8 weeks with each unit lasting 30 min. To ensure that the individual training sessions were performed according to the allocated intensities, they were conducted under the guidance of personal coaches.

Statistical analysis

A mixed-design ANOVA was applied to test for differences between patients with and without fatigue with regard to VO_{2peak} in a pre–post-approach [30]. The significance level was set at $\alpha = 0.05$. Verification of the normal distribution of the outcome variables was performed using the Kolmogorov–Smirnov test. Sphericity of variances was tested using the Mauchly's test. In case of a sphericity violation, a Greenhouse–Geisser correction was performed by adjustment of the degrees of freedom. The homogeneity of group variances was tested using the Bartlett test. Statistic calculations were performed using STATISTICA (Version 12).

A power calculation was performed using g*Power (version 3.1.5) with pPower $[1-\beta] = 80\%$ resulting in a sample size of 34 including possible dropouts. Based on the results of our previous study [11], an effect size (f) of $f = 0.25$ was calculated.

Patients were randomly allocated by simple randomization to both intervention groups resulting in slightly different sample sizes of the HIIT ($n = 22$, 17 females and 5 males) and the MT group ($n = 18$, 14 females, 4 males).

Data were analysed according to the intention-to-treat (ITT) approach. Missing data were substituted using single imputation ("hot deck substitution method with cluster sampling/analysis") with matched age and severity of fatigue. The anthropometric and socio-demographic data of all participants at baseline are shown in Table 1. In addition, baseline data of females and males are shown separately (Table 1). Due to the low numbers of participants, a separate analysis of HIIT and MT according to gender was not performed.

Results

Baseline characteristics and demographic data

At baseline, no significant differences with regard to age, weight, disability, and T25FW were detectable between the total, MT, and HIIT groups. However, baseline VO_{2peak} was significantly higher ($p \leq 0.05$) in the MT (31.9 ± 8.6 ml/min/kg) as opposed to the HIIT group (26.7 ± 6.1 ml/min/kg). The baseline data are summarized in Table 2.

Exercise program

Forty subjects were included in the ITT analysis (Fig. 1). There was a dropout rate of 27.5% over the period of 8 weeks: eleven patients discontinued the study prematurely, five from the HIIT group (three patients with an FSS ≥ 4.0), and six from the MT group (each having an FSS ≥ 4.0). In total, two of the dropouts had an FSS < 4.0 and nine an FSS ≥ 4.0. Reasons for discontinuation of the study were: relapse ($n = 1$), fall (unrelated to the exercise) ($n = 1$), lower back pain ($n = 1$), lack of time ($n = 4$), and no reasons given ($n = 4$).

Training adherence was 73% ± 22% for the entire group (71% ± 22% in the MT and 74% ± 23 in the HIIT group). During the 8 weeks of the study, a total of 24 training units were scheduled for each participant. On average, 17 training units were performed, 17 in the MT, and 18 in the HIIT group.

Outcome parameters

A significant group-by-time effect of VO_{2peak} was detectable in the HIIT group as opposed to the MT group ($p = 0.04$; $f = 0.33$) after the 8 week exercise intervention. By contrast, there was no significant change of the FSS and T25-FW in the entire cohort.

However, sub-group analysis revealed a significant reduction of fatigue in the fatigue group, irrespective of the exercise program, the patients were assigned to. No effects on VO_{2peak} and T25-FW were demonstrated in the fatigue group (Table 3). In the non-fatigue group, none of the aforementioned parameters changed (Table 4).

Although not defined as a primary endpoint of the study, peak power output (PPO) in relation to body weight was included in the descriptive part of the analysis (Tables 1, 2, 3, 4). PPO was neither significantly different in the entire cohort nor in the sub-groups. Of note, PPO in the entire cohort was in the range of healthy untrained individuals [31].

Discussion

VO_{2peak}

Summarizing the previous studies, HIIT can be considered a safe and effective measure to increase VO_{2peak} in MS patients [15]. This finding is supported by the study presented here in which no adverse effects were noted in the context of physical activity. VO_{2peak} increased in the HIIT group but not in the MT group. This physiological adaptation is in line with the effects of HIIT observed in healthy untrained subjects [32, 33]. The fact that no improvement of VO_{2peak} was observed in the MT group

Table 1 Baseline anthropometric and socio-demographic data of study participants

	n	*X*	SD	CI 95%		*p* value
Height (cm)						
Total group	40 (31/9)	172.6 (170.0/182.0)	7.9 (6.2/6.4)	170.1 (167.7/176.7)	175.1 (172.3/186.6)	
HIIT	22 (17/5)	171.4 (168.2/182.2)	8.6 (5.6/8.0)	167.5 (165.2/172.2)	175.2 (171.2/192.2)	n.s
MT	18 (14/4)	174.1 (172.1/181.0)	6.9 (6.1/4.8)	170.7 (168.6/173.3)	177.5 (175.7/188.7)	
BMI (kg/m^2)						
Total group	40 (31/9)	24.3 (23.9/25.7)	4.2 (4.4/3.3)	23.0 (22.3/23.2)	25.7 (25.5/28.2)	
HIIT	22 (17/5)	24.7 (24.4/26.1)	4.7 (5.0/4.0)	22.6 (21.8/21.1)	26.8 (26.9/31.0)	n.s
MT	18 (14/4)	23.8 (23.3/25.3)	3.5 (3.7/2.5)	22.0 (21.2/21.3)	25.5 (25.5/29.3)	
Diagnosis (years)						
Total group	39 (30/9)	10.9 (11.4/9.2)	7.7 (7.1/9.7)	8.4 (8.7/1.8)	13.4 (14.0/16.7)	
HIIT	21 (16/5)	11.1 (12.6/6.2)	7.4 (7.7/3.8)	7.7 (8.6/1.4)	14.5 (16.7/11.0)	n.s
MT	18 (14/4)	10.6 (9.9/13.0)	8.3 (6.5/14.0)	6.5 (6.2/0)	14.7 (13.7/35.0)	
Body weight (kg)						
Total group	40 (31/9)	72.5 (68.9/85.0)	13.7 (11.9/12.4)	68.1 (64.1/75.5)	76.9 (73.2/94.6)	
HIIT	22 (17/5)	72.7 (68.6/86.5)	14.7 (12.6/13.9)	66.2 (62.2/69.2)	79.2 (75.2/103.8)	n.s
MT	18 (14/4)	72.3 (69.1/83.3)	12.7 (11.4/12.1)	66.0 (62.6/64.1)	78.6 (75.7/102.4)	
Age (years)						
Total group	40 (31/9)	42.1 (41.7/43.4)	9.3 (9.4/9.7)	39.1 (38.3/36.0)	45.1 (45.2/50.9)	
HIIT	22 (17/5)	41.6 (41.7/41.2)	9.7 (9.1/12.9)	37.3 (37.1/25.1)	45.9 (46.4/57.3)	n.s
MT	18 (14/4)	42.8 (41.8/46.3)	9.1 (10.1/2.9)	38.2 (36.0/41.7)	47.3 (47.6/50.8)	
FSS						
Total group	40 (31/9)	4.2 (4.3/3.8)	1.2 (1.2/1.4)	3.8 (3.8/2.8)	4.5 (4.7/4.8)	
HIIT	22 (17/5)	4.0 (4.2/3.3)	1.2 (1.2/0.8)	3.5 (3.6/2.3)	4.5 (4.8/4.4)	n.s
MT	18 (14/4)	4.3 (4.3/4.4)	1.3 (1.2/1.8)	3.7 (3.6/1.6)	5.0 (5.0/7.2)	
Descriptive data (part 2/2)						
VO_{2peak} (ml/min/kg)						
Total group	40 (31/9)	29.1 (27.3/35.2)	7.7 (6.9/7.4)	26.6 (24.8/29.5)	31.5 (29.9/40.8)	
HIIT	22 (17/5)	26.7 (25.9/29.8)	6.1 (6.4/4.3)	24.0 (22.6/24.5)	29.4 (29.1/35.1)	*
MT	18 (14/4)	31.9 (29.1/41.9)	8.6 (7.4/3.4)	27.7 (24.9/36.5)	36.2 (33.4/47.3)	
T25-FW (s)						
Total group	40 (31/9)	8.73 (8.80/8.49)	3.23 (3.26/3.32)	7.70 (7.60/5.94)	9.76 (9.99/11.04)	
HIIT	22 (17/5)	8.38 (8.71/7.25)	2.57 (2.61/2.30)	7.24 (7.37/4.39)	9.52 (10.10/10.11)	n.s
MT	18 (14/4)	9.16 (8.90/10.05)	3.93 (4.01/4.05)	7.20 (6.59/3.59)	11.11 (11.22/16.50)	
EDSS						
Total group	34 (27/7)	2.24 (2.29/2.22)	0.85 (1.32/0.71)	1.94 (1.07/1.94)	2.35 (3.51/2.50)	
HIIT	19 (15/4)	2.29 (2.25/2.30)	0.98 (1.66/0.80)	1.82 (0/1.86)	2.76 (4.99/2.74)	n.s
MT	15 (12/3)	2.17 (2.33/2.13)	0.67 (1.04/0.61)	1.79 (0/1.74)	2.54 (4.92/2.51)	
PPO (Watt/kg)						
Total group	40 (31/9)	2.70 (2.66/2.87)	0.81 (0.78/0.92)	2.45 (2.38/2.16)	2.97 (2.95/3.58)	
HIIT	22 (17/5)	2.49 (2.4/2.8)	0.89 (0.87/1.00)	2.09 (1.96/1.51)	2.88 (2.85/4.00)	n.s
MT	18 (14/4)	2.98 (2.97/3.00)	0.61 0.53/0.94)	2.68 (2.77/1.50)	3.28 (3.29/4.51)	

Gender-dependent values are given in brackets (female/male)

BMI body mass index in kg/m^2, *EDSS* expanded disability status scale, *FSS* fatigue severity scale, *Diagnosis (yrs)* number of years since MS diagnosis; *VO_2 peak* (ml/min/kg) Highest measured oxygen consumption in relation to the individual body weight, *T25-FW*: Timed-25 Foot Walk test, *PPO* (Watt/kg) Highest recorded (peak) power output in relation to the individual body weight, *X* arithmetic mean, *SD* standard deviation; *CI 95 % (SD)* Confidence interval of the standard deviation, *ns* not significant, *HIIT* high intensity interval training group, *MT* moderate intensity training group

*Significant differences between groups, $p \leq 0.05$

Table 2 Changes of parameters over the course of time

	n	Diff	SD	CI 95%		*p* value
FSS						
Total group	40	−0.2	0.7	−0.5	0.01	0.07
HIIT	22	−0.3	0.7	−0.7	−0.03	n.s
MT	18	−0.1	0.8	−0.5	0.3	
VO_{2rpeak} (ml/min/kg)						
Total group	40	1.6	4.9	−0.03	3.1	0.07
HIIT	22	3.0	3.6	1.3	4.6	0.04*
MT	18	−0.2	5.9	−3.1	2.7	
T25-FW (s)						
Total group	40	0.04	0.95	−0.3	0.3	n.s
HIIT	22	−0.02	1.22	−0.5	0.6	n.s
MT	18	−0.10	0.49	−0.4	0.1	
PPO (Watt/kg)						
Total group	40	0.12	0.43	−0.02	0.26	n.s
HIIT	22	0.21	0.54	−0.03	0.45	n.s
MT	18	0.01	0.19	−0.09	0.10	

FSS Fatigue Severity Scale, VO_{2peak} (ml/min/kg) highest measured oxygen consumption in relation to the individual body weight, *T25-FW* timed-25 foot walk test, *PPO* (Watt/kg) highest recorded (peak) power output in relation to the individual body weight, *Diff* difference between pre- and post-test, *SD Diff* standard deviation of the difference between pre- and post-test, *CI 95% (SD)* confidence interval of the standard deviation, *HIIT* high-intensity interval training group, *MT* moderate-intensity training group

*p: result of the repeated measurement ANOVA (group × time interaction)

may be explained by the fact that VO_{2peak} at baseline was unexpectedly high, indicating that this particular group of MS patients disposed of an atypically well-developed aerobic fitness. In general, untrained MS patients exhibit a mean VO_{2peak} of 25.5 ± 5.2 ml/min/kg which was improved by endurance training by a mean of 3.5 ml/min/kg [34].

Therefore, it is possible that no further increase in the relative VO_{2peak} could be obtained within this group due to a reduced adaptation capacity as previously shown for MS patients who exhibit abnormally low VO_{2peak} values despite the absence of significant motor deficits and cardiovascular disease [35].

There is as yet no broad consensus with regard to the extent VO_{2peak} needs to be increased to yield clinically significant improvements for MS patients. Kodama et al. demonstrated that an increase of the aerobic capacity by one metabolic equivalent of task (MET) corresponding to a relative increase of VO_{2peak} by approximately 3.5 ml/min/kg results in a 13% reduction of mortality and a 15% reduction of the incidence of cardiovascular diseases [36]. Corresponding to this finding, it has been shown that aerobic fitness is inversely correlated with the risk of cardiovascular co-morbidities in MS patients [37–39].

The results presented here indicate that a mean improvement of VO_{2peak} by 3.0 ml/min/kg may be achieved within 8 weeks of HIIT, demonstrating that HIIT represents a time-efficient manner to increase aerobic fitness.

Fatigue

Sub-group analysis revealed a significant reduction of the FSS in participants with fatigue, while no such changes were detectable in the non-fatigue group. This finding corroborates those of our previous study having demonstrated that patients with fatigue benefit from aerobic exercise [11]. Notably, patients with high baseline fatigue seem to benefit in particular from aerobic exercise [40], a finding which is supported by the results presented here demonstrating high baseline fatigue with a mean FSS score of $X = 5.0$ in the FG.

It remains unclear, however, to what extent fatigue needs to be reduced to become clinically relevant. Whilst a Cochrane review dating back to from 2015 concludes that endurance training results in a significant reduction of fatigue, the authors of a recent randomized-controlled trial were able to reproduce an effect on fatigue but deny its clinical significance [41, 42]. Although validated in numerous trials, the psychometric assessment of fatigue is notoriously difficult and confounded by the subjective perception of MS patients in different stages of their disease [43].

T25-FW

No significant changes were observed in the T25-FW. This finding is not surprising, since the median EDSS in both group was as low as 2.0 indicating no significant

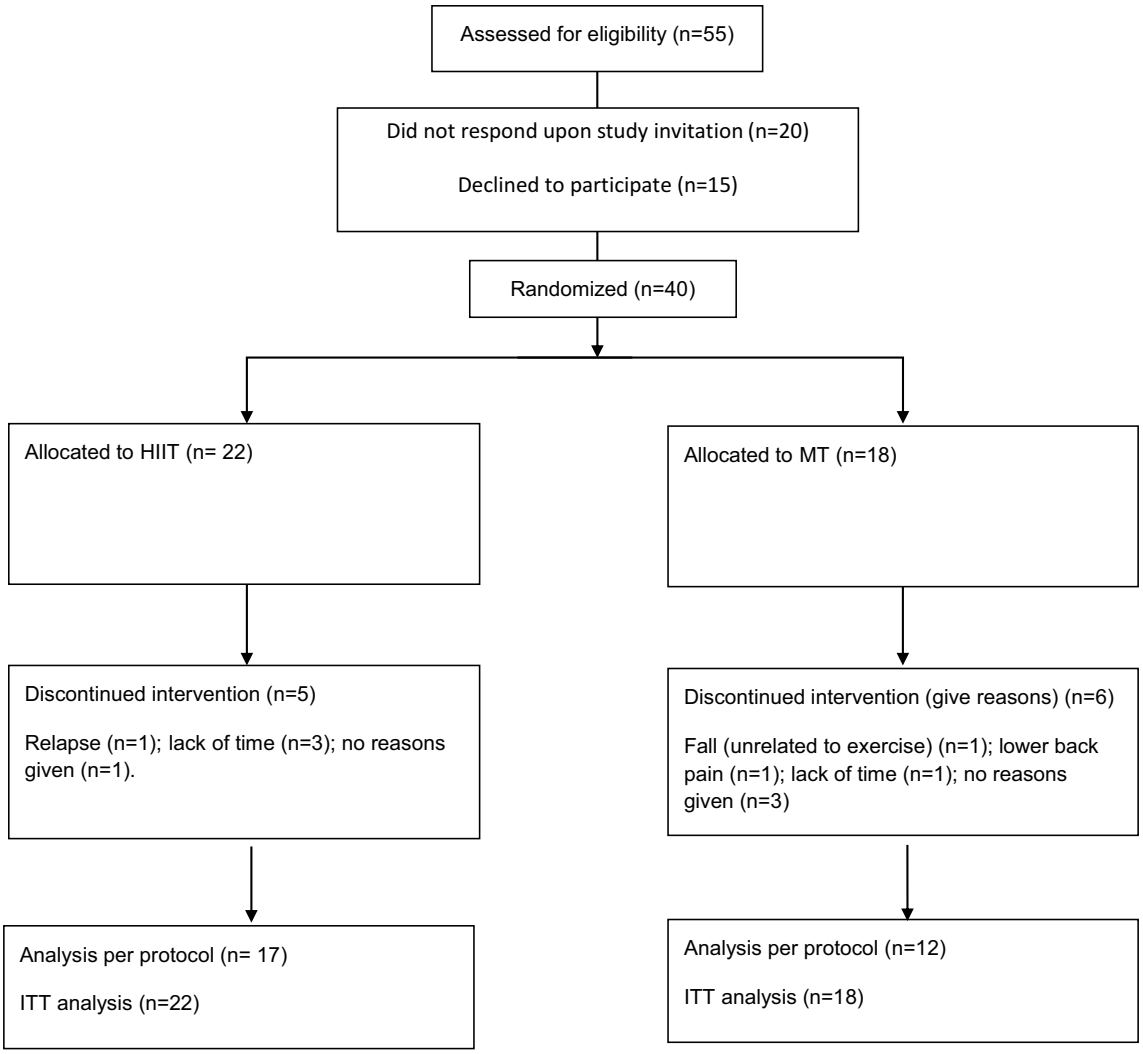

Fig. 1 Flow diagram of study outline

impairment of gait. Moreover, the intervention described here was ergometer-based and not ambulation-based. Therefore, changes in the spatiotemporal ambulatory parameters induced by ambulation-based exercise would not be necessarily expected.

General considerations

The results presented here indicate that HIIT may serve as a time-efficient way to increase VO_{2peak}. In particular, MS patients with very low baseline VO_{2peak} could improve their aerobic capacity within a period of only 8 weeks. This finding is different from the results of our previous study having demonstrated changes in VO_{2peak} and fatigue only after several months of training [11]. In clinical practice, MS patients could start off by improving their aerobic capacity by HIIT within 8 weeks followed by long-term moderate endurance training to maintain these effects. In healthy individuals, the risk for cardiovascular events and the overall mortality are significantly reduced if VO_2 peak reaches 28 ml/min/kg corresponding to 8 MET [36]. Therefore, apart from the effects of HIIT on MS-specific symptoms such as fatigue, the risk for co-morbidities caused by inactivity and sedentary lifestyle might also be reduced, indicating that HIIT might usefully complement moderate aerobic endurance exercise.

Limitations of the study

The interpretation of the data is limited in several aspects. First, dropouts were predominantly patients with fatigue, suggesting that the rather tight schedule with three trainings sessions per week might have been an overexertion to some of the study participants. On the other hand, the dropouts were equally distributed between the HIIT and the MT group still allowing to compare the different exercise regimen in

Table 3 Changes of parameters over the course of time in the sub-group of patients with fatigue

Sub-group analysis—fatigue group						
	n	Diff	SD Diff	CI 95%		*p* value
FSS						
Total sub-group	24	−0.3	0.7	−0.6	−0.03	**0.03**
HIIT	13	−0.4	0.6	−0.8	0.03	n.s
MT	11	−0.2	0.8	−0.8	0.3	
VO_{2peak} (ml/min/kg)						
Total sub-group	24	1.9	5.2	−0.3	4.1	0.10
HIIT	13	3.2	4.0	0.8	5.6	n.s
MT	11	0.3	6.2	−3.9	4.4	
T25-FW (s)						
Total sub-group	24	0.10	0.58	−0.2	0.3	n.s
HIIT	13	0.02	0.68	−0.4	0.4	n.s
MT	11	0.18	0.46	−0.1	0.5	
PPO (Watt/kg)						
Total sub-group	24	0.14	0.49	−0.06	0.35	n.s
HIIT	13	0.29	0.62	−0.08	0.67	n.s
MT	11	−0.03	0.14	−0.13	0.06	

Bold value indicates a significant reduction in fatigue over time

BMI body mass index in kg/m^2, *FSS* Fatigue Severity Scale, *nFG* non-fatigue group, *FG* fatigue group, *VO_{2peak}* (ml/min/kg) highest measured oxygen consumption in relation to the individual body weight, *T25-FW* timed-25 foot walk test, *PPO* (Watt/kg) highest recorded (peak) power output in relation to the individual body weight, *Diff* difference between pre- and post-test, *SD Diff* standard deviation of the difference between pre- and post-test, *CI 95% (SD)* confidence interval of the standard deviation, *p* result of the repeated measurement ANOVA (main effect of time), *HIIT* high-intensity interval training group, *MT* moderate-intensity training group

Table 4 Changes of parameters over the course of time in the sub-group of patients without fatigue

Sub-group analysis—non-fatigue group						
	n	Diff	SD diff	CI 95% (SD)		*p* value
FSS						
Total sub-group	16	−0.1	0.8	−0.5	0.3	n.s
HIIT	9	−0.2	0.7	−0.9	0.4	n.s
MT	7	0.1	0.8	−0.6	0.8	
VO_2(ml/min/kg)						
Total sub-group	16	1.1	4.7	−1.4	3.6	n.s
HIIT	9	2.6	3.2	0.1	5.1	n.s
MT	7	−0.9	5.7	−6.1	4.4	
T25-FW (sec)						
Total sub-group	16	−0.05	1.35	−0.8	0.7	n.s
HIIT	9	−0.08	1.78	−1.5	1.3	n.s
MT	7	−0.03	0.54	−0.5	0.5	
PPO (Watt/kg)						
Total sub-group	16	0.08	0.34	−0.10	0.26	n.s
HIIT	9	0.09	0.42	−0.23	0.41	n.s
MT	7	0.07	0.24	−0.16	0.29	

BMI body mass index in kg/m^2, *FSS* Fatigue Severity Scale, *nFG* non-fatigue group, *FG* fatigue group, *VO_{2peak}* (ml/min/kg) highest measured oxygen consumption in relation to the individual body weight, *T25-FW* timed-25 foot walk test, *PPO* (Watt/kg) highest recorded (peak) power output in relation to the individual body weight, *p* result of the repeated measurement ANOVA (group x time interaction), *Diff* difference between pre- and post-test, *SD Diff* standard deviation of the difference between pre- and post-test, *CI 95% (SD)* confidence interval of the standard deviation, *HIIT* high-intensity interval training group, *MT* moderate-intensity training group

the two groups. Second, there was a significant difference in aerobic fitness at baseline within the two trainings groups.

To ensure that the pre-calculated number of patients could be recruited for the study, both females and males were accepted for participation. As a consequence, the inclusion of four male MS patients contributed to the significantly higher baseline VO_{2peak} in the MT group, although the relative proportion of male patients in both groups was 30%. Moreover, simple randomization resulted in a higher number of participants in the HIIT group.

Nonetheless, we believe that the main effect of improving VO_{2peak} by HIIT within a comparatively short period of time is consistent with the previous findings [18, 19] despite the aforementioned methodological shortcomings.

Conclusions

In summary, HIIT may be a promising and time-efficient approach in MS patients to improve aerobic fitness and decrease fatigue in patients with elevated baseline fatigue. Moreover, HIIT performed on a stationary ergometer represents an easy-to perform and safe method of endurance exercise in MS patients. Further studies are warranted tailoring the exercise regimes to the individual patients´ needs and capacities to better understand the effects of improved VO_{2peak} by HIIT on fatigue in MS patients.

Acknowledgements Not applicable.

Funding This study was supported by a research grant from Bayer Vital (Grant PB05). The sponsor has neither taken influence on the preparation of the article nor on the collection, analysis, and interpretation of data.

Compliance with ethical standards

Conflict of interests Both authors have received compensations from Bayer Vital for lecturing. S.Schmidt has also served on advisory boards for Bayer Vital.

Ethical approval All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Deutsche Sporthochschule, Cologne, Germany.

Informed consent All participants gave written informed consent prior to study participation.

References

1. Klaren RE, Motl RW, Dlugonski D et al (2013) Objectively quantified physical activity in persons with multiple sclerosis. Arch Phys Med Rehabil 94(12):2342–2348. https://doi.org/10.1016/j.apmr.2013.07.011
2. Sandroff BM, Dlugonski D, Weikert M et al (2012) Physical activity and multiple sclerosis: new insights regarding inactivity. Acta Neurol Scand 126(4):256–262. https://doi.org/10.1111/j.1600-0404.2011.01634.x
3. Béthoux F (2006) Fatigue et sclérose en plaques. Annales de Réadaptation et de Médecine Physique 49(6): 265–271. https://doi.org/10.1016/j.annrmp.2006.04.023
4. Kayes NM, McPherson KM, Taylor D et al (2011) Facilitators and barriers to engagement in physical activity for people with multiple sclerosis: a qualitative investigation. Disabil Rehabil 33(8):625–642. https://doi.org/10.3109/09638288.2010.505992
5. Motl RW, Pilutti LA (2012) The benefits of exercise training in multiple sclerosis. Nat Rev Neurol 8(9):487–497. https://doi.org/10.1038/nrneurol.2012.136
6. Pilutti LA, Greenlee TA, Motl RW et al (2013) Effects of exercise training on fatigue in multiple sclerosis: a meta-analysis. Psychosom Med 75(6):575–580. https://doi.org/10.1097/PSY.0b013e31829b4525
7. Bjarnadottir OH, Konradsdottir AD, Reynisdottir K et al (2007) Multiple sclerosis and brief moderate exercise. A randomised study. Mult Scler 13(6):776–782. https://doi.org/10.1177/1352458506073780
8. Petajan JH, Gappmaier E, White AT et al (1996) Impact of aerobic training on fitness and quality of life in multiple sclerosis. Ann Neurol 39(4):432–441. https://doi.org/10.1002/ana.410390405
9. Ponichtera-Mulcare JA (1993) Exercise and multiple sclerosis. Med Sci Sports Exerc 25(4):451–465
10. Rampello A, Franceschini M, Piepoli M et al (2007) Effect of aerobic training on walking capacity and maximal exercise tolerance in patients with multiple sclerosis: a randomized crossover controlled study. Phys Ther 87(5):545–555. https://doi.org/10.2522/ptj.20060085
11. Schmidt S, Wonneberger M (2014) Long-term endurance exercise improves aerobic capacity in patients with relapsing-remitting multiple sclerosis: impact of baseline fatigue. J Neurol Sci 336(1–2):29–35. https://doi.org/10.1016/j.jns.2013.09.035
12. Gormley SE, Swain DP, High R et al (2008) Effect of intensity of aerobic training on VO_{2max}. Med Sci Sports Exerc 40(7):1336–1343. https://doi.org/10.1249/MSS.0b013e31816c4839
13. Helgerud J, Høydal K, Wang E et al (2007) Aerobic high-intensity intervals improve VO_{2max} more than moderate training. Med Sci Sports Exerc 39(4):665–671. https://doi.org/10.1249/mss.0b013e3180304570
14. Shiraev T, Barclay G (2012) Evidence based exercise—clinical benefits of high intensity interval training. Aust Fam Physician 41(12):960–962
15. Campbell E, Coulter EH, Paul L (2018) High intensity interval training for people with multiple sclerosis: a systematic review. Mult Scler Relat Disord 24:55–63. https://doi.org/10.1016/j.msard.2018.06.005
16. Wens I, Dalgas U, Vandenabeele F et al (2015) High intensity exercise in multiple sclerosis: effects on muscle contractile characteristics and exercise capacity, a randomised controlled trial. PLoS One 10(9):e0133697. https://doi.org/10.1371/journal.pone.0133697
17. Collett J, Dawes H, Meaney A et al (2011) Exercise for multiple sclerosis: a single-blind randomized trial comparing three exercise intensities. Mult Scler J 17(5):594–603. https://doi.org/10.1177/1352458510391836
18. Ross LM, Porter RR, Durstine JL (2016) High-intensity interval training (HIIT) for patients with chronic diseases. J Sport Health Sci 5(2):139–144. https://doi.org/10.1016/j.jshs.2016.04.005
19. Liou K, Ho S, Fildes J et al (2016) High intensity interval versus moderate intensity continuous training in patients with

coronary artery disease: a meta-analysis of physiological and clinical parameters. Heart Lung Circ 25(2):166–174. https://doi.org/10.1016/j.hlc.2015.06.828
20. Polman CH, Reingold SC, Banwell B et al (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 69(2):292–302. https://doi.org/10.1002/ana.22366
21. Fletcher GF, Balady GJ, Amsterdam EA et al (2001) Exercise standards for testing and training: a statement for healthcare professionals From the American Heart Association. Circulation 104(14):1694–1740. https://doi.org/10.1161/hc3901.095960
22. Appell H-J (2002) Lehrbuch der Sportmedizin, Unveränd. Nachdr. Dt. Ärzte-Verl., Köln
23. Wonisch M, Hofmann P, Pokan R et al (2003) Spiroergometrie in der Kardiologie—Grundlagen der Physiologie und Terminologie. Journal für Kardiologie 10(9):383–390
24. Krupp LB, LaRocca NG, Muir-Nash J et al (1989) The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 46(10):1121–1123
25. Whitehead L (2009) The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. J Pain Symptom Manage 37(1):107–128. https://doi.org/10.1016/j.jpainsymman.2007.08.019
26. Polman CH, Rudick RA (2010) The multiple sclerosis functional composite: a clinically meaningful measure of disability. Neurology 74 (Suppl 3):S8–S15. https://doi.org/10.1212/WNL.0b013e3181dbb571
27. Motl RW, Cohen JA, Benedict R et al (2017) Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. Mult Scler 23(5):704–710. https://doi.org/10.1177/1352458517690823
28. Lerdal A, Wahl A, Rustøen T et al (2005) Fatigue in the general population: A translation and test of the psychometric properties of the Norwegian version of the fatigue severity scale. Scand J Public Health 33(2):123–130. https://doi.org/10.1080/14034940410028406
29. Rosti-Otajärvi E, Hämäläinen P, Wiksten A et al (2017) Validity and reliability of the fatigue severity scale in finnish multiple sclerosis patients. Brain Behav 7(7):e00743. https://doi.org/10.1002/brb3.743
30. Bühner M, Ziegler M (2009) Statistik für Psychologen und Sozialwissenschaftler. Pearson Studium, München
31. Rost R (2005) Sport- und Bewegungstherapie bei Inneren Krankheiten: Lehrbuch für Sportlehrer, Übungsleiter, Physiotherapeuten und Sportmediziner, 3. Aufl. komplett überarb. und erw. von B. Bjarnason-Wehrens (and others). Deutscher Ärzte-Verlag, Köln
32. Weston KS, Wisloff U, Coombes JS (2014) High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. Br J Sports Med 48(16):1227–1234. https://doi.org/10.1136/bjsports-2013-092576
33. Koufaki P, Mercer TH, George KP et al (2014) Low-volume high-intensity interval training vs continuous aerobic cycling in patients with chronic heart failure: a pragmatic randomised clinical trial of feasibility and effectiveness. J Rehabil Med 46(4):348–356. https://doi.org/10.2340/16501977-1278
34. Langeskov-Christensen M, Heine M, Kwakkel G et al (2015) Aerobic capacity in persons with multiple sclerosis: a systematic review and meta-analysis. Sports Med 45(6):905–923. https://doi.org/10.1007/s40279-015-0307-x
35. Wonneberger M, Schmidt S (2015) Changes of gait parameters following long-term aerobic endurance exercise in mildly disabled multiple sclerosis patients: an exploratory study. Eur J Phys Rehabil Med 51(6):755–762
36. Kodama S, Saito K, Tanaka S et al (2009) Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA 301(19):2024–2035. https://doi.org/10.1001/jama.2009.681
37. Marrie R, Horwitz R, Cutter G et al (2009) High frequency of adverse health behaviors in multiple sclerosis. Mult Scler 15(1):105–113. https://doi.org/10.1177/1352458508096680
38. Marrie R, Horwitz R, Cutter G et al (2008) Comorbidity, socioeconomic status and multiple sclerosis. Mult Scler 14(8):1091–1098. https://doi.org/10.1177/1352458508092263
39. Heine M, Wens I, Langeskov-Christensen M et al (2016) Cardiopulmonary fitness is related to disease severity in multiple sclerosis. Mult Scler 22(2):231–238. https://doi.org/10.1177/1352458515581437
40. Andreasen A, Stenager E, Dalgas U (2011) The effect of exercise therapy on fatigue in multiple sclerosis. Mult Scler J 17(9):1041–1054. https://doi.org/10.1177/1352458511401120
41. Heine M, Verschuren O, Hoogervorst ELJ et al (2017) Does aerobic training alleviate fatigue and improve societal participation in patients with multiple sclerosis? A randomized controlled trial. Mult Scler 23(11):1517–1526. https://doi.org/10.1177/1352458517696596
42. Heine M, van de Port I, Rietberg MB et al (2015) Exercise therapy for fatigue in multiple sclerosis. Cochrane Database Syst Rev 9:CD009956. https://doi.org/10.1002/14651858.CD009956.pub2
43. Langeskov-Christensen M, Bisson EJ, Finlayson ML et al (2017) Potential pathophysiological pathways that can explain the positive effects of exercise on fatigue in multiple sclerosis: A scoping review. J Neurol Sci 373:307–320. https://doi.org/10.1016/j.jns.2017.01.002