High-intensity interval exercise improves cognitive performance and reduces matrix metalloproteinases-2 serum levels in persons with multiple sclerosis: A randomized controlled tri...

Article *in* Multiple Sclerosis · August 2017

DOI: 10.1177/1352458517728342

CITATIONS
21

READS
654

10 authors, including:

Philipp Zimmer
German Sport University Cologne and German Cancer Research Center, Heidelberg
87 PUBLICATIONS **420** CITATIONS
SEE PROFILE

Alexander Schenk
Deutsche Sporthochschule Köln
30 PUBLICATIONS **210** CITATIONS
SEE PROFILE

Max Oberste
Deutsche Sporthochschule Köln
29 PUBLICATIONS **119** CITATIONS
SEE PROFILE

Jan Kool
Kliniken Valens
211 PUBLICATIONS **1,416** CITATIONS
SEE PROFILE

MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

High-intensity interval exercise improves cognitive performance and reduces matrix metalloproteinases-2 serum levels in persons with multiple sclerosis: A randomized controlled trial

Philipp Zimmer, Wilhelm Bloch, Alexander Schenk, Max Oberste, Stefan Riedel, Jan Kool, Dawn Langdon, Ulrik Dalgas, Jürg Kesselring and Jens Bansi

Multiple Sclerosis Journal

1–10

DOI: 10.1177/1352458517728342

Abstract

Background: Aerobic exercise can improve cognitive performance in healthy elderly people.

Objective: The aim of this study was to investigate the influence of a 3-week high-intensity aerobic exercise programme (high-intensity training group (HIT)) on cognitive performance in persons with multiple sclerosis (MS) compared with a standard exercise programme (control training (CT)).

Methods: A total of 60 persons with MS (Expanded Disability Status Scale (EDSS): 1.0–6.5) were randomized to a HIT group (3×/week for 20 minutes, including five 3-minute exercise intervals at 80% of peak oxygen uptake ($VO_{2\text{-peak}}$)) or a CT group (continuously 5×/week for 30 minutes/session at 65% of $VO_{2\text{-peak}}$). Cognitive performance was assessed using the Brief International Cognitive Assessment for MS at entry (t_0) and discharge (t_1). Furthermore, $VO_{2\text{-peak}}$, brain-derived neurotrophic factor, serotonin and matrix metalloproteinases (MMP)-2 and -9 were measured.

Results: Compared to CT, HIT significantly improved verbal memory. Significant improvements over time in executive functions were found in both groups. Secondary outcomes indicated significant improvements in $VO_{2\text{-peak}}$ and a significant reduction in MMP-2 in the HIT group only.

Conclusion:: HIT represents a promising strategy to improve verbal memory and physical fitness in persons with MS. Further research is needed to determine the impact of exercise on biomarkers in MS.

Keywords: Exercise, cognition, multiple sclerosis

Date received: 27 April 2017; revised: 24 July 2017; accepted: 26 July 2017

Correspondence to:
P Zimmer
Department for Molecular and Cellular Sports Medicine, German Sport University Cologne, Am Sportpark Müngersdorf 6, 50933 Cologne, Germany.
p.zimmer@dshs-koeln.de

Philipp Zimmer
Department for Molecular and Cellular Sports Medicine, German Sport University Cologne, Cologne, Germany/ National Center for Tumor Diseases (NCT) and German Cancer Research Center, Heidelberg, Germany

Wilhelm Bloch
Alexander Schenk
Max Oberste
Department for Molecular and Cellular Sports Medicine, German Sport University Cologne, Cologne, Germany

Stefan Riedel
ARIGNOS, Dresden, Germany

Jan Kool
Jürg Kesselring
Jens Bansi
Department of Neurology, Kliniken Valens, Valens, Switzerland

Dawn Langdon
Royal Holloway, University of London, Egham, UK

Ulrik Dalgas
Section for Sport Science, Department of Public Health, Aarhus University, Aarhus, Denmark

Introduction

Persons with multiple sclerosis (pwMS) progressively develop impaired functional and cognitive capacity and reduced physical activity. Cognitive impairments occur in 43%–70% of pwMS, leading to slow mental processing speed and impaired memory.[1]

Exercise programmes for pwMS have been described as promising supportive therapy options for reducing symptoms and side-effects of multiple sclerosis (MS).[2–4] Regular exercise is known to induce physiological, structural and functional adaptations of the central nervous system (CNS). At the physiological level, these effects comprise an increase in neurotrophic factors and neurotransmitters and a reduction in inflammatory markers on the CNS.[5–7] Moreover, exercise-induced alterations in levels of matrix metalloproteinases (MMP) that are known to play a crucial role in the function of the blood–brain barrier and the pathogenesis of MS are suggested.[8–11] In view of structural adaptations of the CNS in response to exercise, an increase in grey and white matter has been shown in healthy controls and

pwMS.[12] Specific brain regions, such as the hippocampus, are highly responsive to exercise stimuli, due to the increase in neurotrophic factors.[12] In addition, brain-derived neurotrophic factor (BDNF) has been suggested to improve synaptic plasticity and to have neuroprotective properties.[5] On a functional level, exercise is known to improve cognitive performance in healthy ageing populations, in terms of executive functions and memory.[13]

Few studies have investigated the effects of exercise programmes on cognitive functions in pwMS. The existing results are contradictory and hardly comparable, due to numerous methodological limitations, such as very small sample sizes, the lack of adequate control groups, varying assessments and exercise modalities.[4,14] Furthermore, only two randomized controlled trials (RCTs), including appropriate sample size calculation, use cognitive performance as primary endpoint. Oken et al.[15] reported no effects of low-intensity exercise or yoga on cognitive performance, whereas Sandroff et al.[16] have shown improved cognitive function in pwMS who have participated in a theory-based programme for increasing physical activity.

In clinical/rehabilitative settings, exercise programmes are conducted at low-to-moderate intensity in order not to overburden patients. Today, we know that intensive exercise interventions with adequate regeneration periods are feasible, safe and well tolerated with different patient groups, including pwMS.[17] Research in the past decade suggests that high-intensity training group (HIT) endurance exercise is more efficient in terms of increasing cardiorespiratory fitness and in provoking physiological adaptations compared to constant low-to-moderate endurance exercise.[18,19] Since increased levels of cardiorespiratory fitness have been reported to be associated with better cognitive performance in several clinical populations, HIT may represent a promising strategy to improve cognitive performance in pwMS.[20] Furthermore, HIT programmes are time efficient and less monotonous.

The primary aim of this study was to test the hypothesis that a 3-week HIT endurance exercise programme during inpatient rehabilitation can improve cognitive performance in pwMS compared to a conventional moderate aerobic exercise programme. A secondary aim was to evaluate whether the exercise programmes differentially influenced basal serum levels of BDNF, serotonin, MMP-2 and MMP-9.

Materials and methods

Study design

This RCT with blinded outcome assessment evaluated a 3-week training intervention to determine the effect of exercise on cognitive performance in persons with relapsing–remitting and secondary progressive MS. All measurements and testing of this two-arm RCT were determined at entry (t_0) and discharge (t_1) to the 3-week exercise programme. Blood samples were taken for analysis of serum levels of serotonin and BDNF, then participants completed a neuropsychological test battery, followed by questionnaires and a cardiopulmonary exercise test (CPET).

The study was approved by the regional scientific ethics committee (EKOS 15/090), was registered at ClinicalTrials.gov (NCT02571335) before recruitment started and complied with the principles of the Declaration of Helsinki.

Participants

Inpatients assigned for rehabilitation at the Valens clinic, Switzerland, holding a definite MS diagnosis (revised McDonald criteria)[21] were screened for inclusion on the day of clinical admission over an 8-month period. A total of 106 persons with a relapsing–remitting and secondary progressive disease course fulfilled the main study criteria of an Expanded Disability Status Scale (EDSS) score between 1.0 and 6.5 and age >30 years. Participants underwent general medical screening for study eligibility and were excluded if persistent infections, cardiovascular or pulmonary diseases were evident, neurodegenerative disorders other than MS were diagnosed or had severe disease progression/relapses the day prior to CPET. During the study, treatments involving the study procedures were interrupted if participants had acute relapses. Participants who were given immune-modulating medication the day prior to CPET were not assigned for blood sampling at any time point; however, other assessments involving the study were continued. All participants had physician clearance, were informed about the study, and gave their written consent before the study started.

Randomization and masking

A total of 60 patients were eligible for inclusion. A concealed randomization procedure was carried out, and participants were allocated to a HIT group ($n = 29$) or a moderate-intensity control training (CT) group ($n = 31$). Cardiorespiratory fitness (assessed by CPET) and cognitive fatigue (assessed by the Fatigue Scale for Motor and Cognitive Functions (FSMC)) were

used as stratification factors. Independent physiotherapists supervised the training within both groups. The principal investigator conducting CPET and data analysis and the psychologist who performed cognitive testing were blinded to the training.

Treatments

HIT comprised five 3-minute physiologically high-intensity intervals of cycling at 80–100 r/min (85%–90% of maximum heart rate (HR_{max}) or 80% of peak oxygen uptake ($VO_{2\text{-peak}}$). During intervals, the cadence was reduced to 50–60 r/min for 1.5 minutes to reduce heart rate to 50%–60% of HR_{max}. The duration of the training session was 20 minutes, with a warm-up and cool-down for the first and the last 2 minutes, respectively. A 45-minute recovery time after the training session was included in the programme. Three training sessions were conducted per week.

CT consisted of physiologically defined heart rate controlled cycling at 60 r/min at the lactate threshold (70% of HR_{max} or 65% of $VO_{2\text{-peak}}$). A training session lasted 30 minutes, with warm-up and cool-down for the first and last 2 minutes, respectively. A total of five training sessions were conducted per week. CT represents usual care in the rehabilitation centre.

Adherence to HIT and CT was determined by the following quotient: completed exercise sessions/total number of planned exercise sessions.

Cardiopulmonary exercise testing

All participants performed graded CPET on a cycle ergometer (Ergoline Ergoselect 200; Ergoline GMBH, Bitz, Germany) at entry and discharge in order to determine cardiorespiratory fitness ($VO_{2\text{-peak}}$) as previously reported by Bansi et al.[22]

Confounding factors

Intelligence was assessed using the Multiple Choice Vocabulary Test Version A (MWT-A).[23] Depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS).[24] Fatigue was determined using the German version of the multidimensional (FSMC).[25]

Neuropsychological assessment

Neuropsychological assessments included the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS),[1] the Trail-Making (pencil) Test (TMT-A/B)[26] and Go/No Go tasks of the Test Battery of Attention Performance (TAP).[27] The BICAMS test battery involves three tests assessing the main cognitive domains vulnerable to MS: information processing speed, verbal and visual memory. The battery includes the Symbol Digit Modalities Test (SDMT),[28] Californian Verbal Learning Test-II (CVLT-II)[29] and the Brief Visuospatial Memory Test–Revised (BVMT-R).[30] Parallel versions were used for all neuropsychological assessments at t_0 and t_1.

Serum levels of serotonin, BDNF, MMP-2 and MMP-9

Resting blood samples were taken from the antecubital vein. Samples were centrifuged at 3000 g for 10 minutes at 4°C, and the supernatant was stored at –40°C until analysis. Serum concentrations of BDNF, MMP-2 and MMP-9 were determined by enzyme-linked immune sorbent assay (ELISA) (R&D Systems, Inc., Minneapolis, MN, USA) according to the manufacturer's instructions. Serum serotonin was measured by high-performance liquid chromatography (HPLC) with colorimetric detection (Agilent HP 1200; Agilent Technologies, Santa Clara, CA, USA).

Statistical analysis

Sample size calculation was performed using G*power software (University of Düsseldorf, Düsseldorf, Germany). Moderate effects of exercise interventions on higher cognitive functions have been reported.[5] Thus, a small-to-moderate effect following Cohens' classification ($f = 0.2$) was used for power analysis. Statistical test-power was set at 0.80 and significance level (α) at 0.05. Correlation of participants' test scores at t_0 and at t_1 was estimated at $r = 0.5$. Power analysis was conducted to detect any interaction effects between within-subjects factor time point (t_0 vs t_1) and between-subjects factor treatment (HIT vs CT) on cognitive testing performance using a 2×2 mixed analysis of variance (mixed ANOVA). To achieve statistical test-power, 52 participants were required. The expected drop-out rate was 15%; therefore, we aimed to include 60 participants in the study.

Baseline differences regarding the distribution of anthropometric data, cognitive impairments (poor performance (>1 standard deviation (SD) compared to healthy, age matched norm data) in at least one of the three BICAMS tests or the TMT A/B), fitness ($VO_{2\text{-peak}}$), intelligence, depression, fatigue and disability levels (EDSsS) were investigated using independent *t*-tests and Fisher's exact tests. Differences

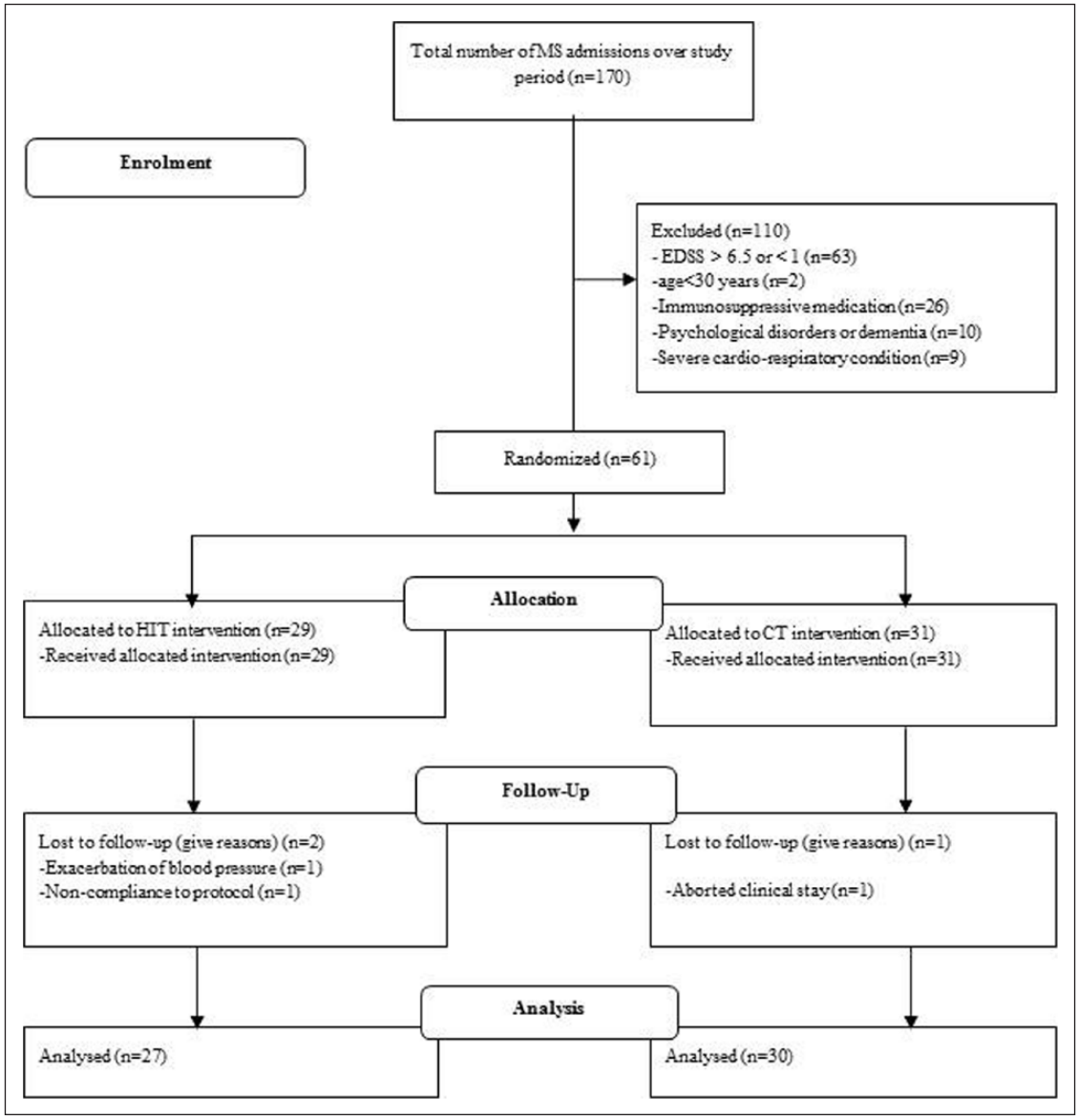

Figure 1. Trial profile.

for all endpoints were analysed by 2 × 2 ANOVA (intention-to-treat). ANOVA results are presented as p values, F (df) and effect sizes (partial η^2) for the main factors 'time' and 'group' and their interaction (time × group). Within-subjects factor time point was investigated for both groups (simple effects analysis (SEA)). Alpha error accumulation at SEA was controlled using the Bonferroni adjustment. Correlation analysis (Pearson for metric data and Spearman for ordinal data) was conducted to assess associations between fitness and cognitive performance at both measurement time points and for the potential changes. Significance was defined as p value <0.05. All statistical analyses were conducted using SPSS 22® (IBM®, Armonk, NY, USA).

Results

Between 1 September 2015 and 31 May 2016, 60 patients were included, and 57 completed the study, with a completion rate of 95%. No adverse events occurred. In the HIT, two participants dropped-out: one had blood pressure exacerbations, and the other was non-compliant with the exercise protocol. In CT, one participant was lost to follow-up as he discharged himself from the clinic. The trial profile is shown in Figure 1. All 57 participants who completed the study indicated an adherence (number of successfully conducted exercise sessions) of 100%.

Participants' characteristics are listed in Table 1. No baseline differences between groups were found. In

Table 1. Study participants' baseline characteristics.

	HIT ($n=27$)	CT ($n=30$)
Sex	F: 20 (74%); M: 7 (26%)	F: 18 (60%); M: 12 (40%)
Age (years)	51 (9.9)	48 (12.1)
Disease severity (RRMS/SPMS)	14/13	16/14
Years since diagnosis	Total 11.98 ± 11.34 RRMS 10.75 ± 8.75 SPMS 13.31 ± 13.86	13.33 ± 9.3 RRMS 11.69 ± 7.17 SPMS 15.21 ± 11.31
BMI (kg/m^2)	22.55 (2.65)	23.73 (4.80)
Cognitive impairments	16 (59.3%)	17 (56.6%)
$VO_{2\text{-peak}}$ (mL kg^{-1} min^{-1})	20.03 (5.88)	19.03 (6.14)
EDSS score	4.37 (1.39)	4.37 (0.98)
Intelligence (MWT score)	28.63 (4.93)	28.11 (3.76)
Anxiety/depression (HADS score)	6.41 (3.95)	9.33 (7.45)
Fatigue (FSMC score)	64.74 (14.69)	62.17 (14.18)

HIT: high-intensity training group; CT: control training group; F: female; M: male; RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; BMI: body mass index; Cognitive impairments: reduced performance in at least one of the three Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) assessments; EDSS: Expanded Disability Status Scale; MWT: Multiple Choice Vocabulary Test; HADS: Hospital Anxiety and Depression Scale; FSMC: Fatigue Scale for Motor and Cognitive Functions. Endurance capacity: $VO_{2\text{-peak}}$ data are presented as means (standard deviation).

total, 57.9% of study participants indicated cognitive impairments.

ANOVA results are listed in Table 2. ANOVA revealed no differences between groups. Significant improvements over time (time effects) were found for processing speed (SDMT), cognitive flexibility/task shifting (TMT B), response inhibition (TAP errors) and cardiorespiratory fitness ($VO_{2\text{-peak}}$). Interaction effects (time × group) showed significant differences for verbal memory (Verbal Learning and Memory Test (VLMT)), cardiorespiratory fitness ($VO_{2\text{-peak}}$) and serum MMP-2 levels.

Subsequent SEA showed significant improvement of verbal memory in the HIT ($p=0.046$, 95% confidence interval (CI) (–6.319; –0.51)), whereas no alterations were found in CT ($p=0.316$, 95% CI (–1.473; 4.473)). Cardiorespiratory fitness increased significantly in both groups (HIT: $p<0.001$, 95% CI (–4.096; –2.002); CT: ($p=0.006$, 95% CI (–2.394; –0.426)) being higher in the HIT. Serum levels of MMP-2 decreased significantly in HIT ($p=0.009$, 95% CI (5.336; 36.587)), whereas no changes were detected in the CT ($p=0.305$, 95% CI (–22.470; 7.169)). Response inhibition (TAP errors) showed a tendency for interaction effects, and SEA was also conducted indicating significant improvements in test performance for HIT (HIT: $p=0.001$, 95% CI (0.508; 1.789); CT: $p=0.327$, (–0.308; 0.908)) (Figure 2(a)–(d)).

Correlation analysis revealed significant correlations between $VO_{2\text{-peak}}$ and cognitive performance in some cognitive domains at t_0 (SDMT: $r=0.292$; $p=0.027$, VLMT: $r=0.281$; $p=0.034$) and at t_1 (SDMT: $r=0.271$; $p=0.042$, VLMT: $r=0.244$; $p=0.068$, TMT A: $r=-0.316$; $p=0.017$, TMT B: $r=-0.333$; $p=0.011$, TAP errors: $r=-0.283$; $p=0.033$), whereas changes in VO_2-peak showed no association with changes in cognitive performance (SDMT: $r=-0.149$; $p=0.270$, VLMT: $r=0.086$; $p=0.526$, BVMT-R: $r=0.074$; $p=0.586$, TMT A: $r=0.011$; $p=0.938$, TMT B: $r=0.181$; $p=0.178$, TAP time: $r=0.145$; $p=0.283$, TAP errors: $r=-0.049$; $p=0.719$). However, changes in $VO_{2\text{-peak}}$ indicated a negative association with serum MMP-2 levels ($r=-0.310$; $p=0.019$).

Discussion

This is the first RCT comparing the effects of HIT with a usual moderate-intensity exercise programme on cognitive performance, cardiorespiratory fitness, and associated blood parameters serotonin and BDNF in pwMS. The results suggest that HIT improves verbal memory in pwMS during 3-week inpatient rehabilitation. Participants showed no adverse effects towards HIT and the testing protocols. HIT led to a decrease in serum concentrations of MMP-2.

To date, only few RCTs included 'cognitive performance' as primary endpoint. A recent meta-analysis[4] reports contradictory results. Studies that examine the effects of exercise on cognitive performance in pwMS are not comparable, since different exercise modalities (type, intensity, duration) and varying cognitive

Table 2. Analysis of variance (ANOVA) results for all outcomes.

	HIT ($n=27$)		CT ($n=30$)		ANOVA		
	t_0 mean (SD)	t_1 mean (SD)	t_0 mean (SD)	t_1 mean (SD)	Group p value F (df = 1) partial η^2	Time p value F (df = 1) partial η^2	Group × time p value F, (df = 1) partial η^2
SDMT	41.556 (11.617)	44.963 (13.993)	41.833 (11.709)	44.333 (11.547)	0.955 0.003 0.000	0.001[a] 12.686 0.187	0.587 0.299 0.005
VLMT recall 1–5 words	52.074 (11.799)	55.259 (9.529)	50.800 (11.025)	49.300 (11.271)	0.186 1.798 0.032	0.438 0.611 0.011	0.034[a] 4.724 0.079
BVMT-R total	24.22 (6.991)	23.593 (6.159)	22.167 (7.839)	22.967 (7.059)	0.446 0.590 0.011	0.901 0.016 0.000	0.298 1.104 0.020
TMT A (s)	47.370 (24.520)	40.741 (22.424)	47.900 (23.143)	48.900 (22.439)	0.448 0.583 0.010	0.226 1.496 0.026	0.103 2.748 0.048
TMT B (s)	107.815 (53.903)	93.259 (45.041)	127.900 (67.824)	109.533 (59.351)	0.225 1.503 0.027	<0.001[a] 20.938 0.276	0.598 0.281 0.005
TAP time (ms)	472.593 (77.002)	463.815 (84.020)	460.033 (92.646)	464.133 (120.866)	0.792 0.070 0.001	0.826 0.049 0.001	0.547 0.368 0.007
TAP (errors)	1.676 (1.981)	0.519 (0.753)	1.533 (2.300)	1.233 (2.046)	0.520 0.419 0.008	0.002[a] 10.804 0.164	0.059 3.706 0.063
$VO_{2\text{-peak}}$ ($mL\,kg^{-1}\,min^{-1}$)	20.033 (5.876)	23.093 (6.632)	19.027 (6.137)	20.437 (5.807)	0.252 1.340 0.024	<0.001[a] 39.261 0.417	0.025[a] 5.346 0.089
BDNF (ng/mL)	20.965 (10.606)	24.663 (13.019)	19.286 (11.234)	20.858 (10.166)	0.250 1.351 0.024	0.158 2.053 0.036	0.566 0.344 0.006
Serotonin (µg/L)	105.333 (80.795)	128.070 (81.493)	166.090 (152.390)	178.827 (185.095)	0.098 2.837 0.049	0.203 1.659 0.029	0.718 0.132 0.002
MMP-2 (ng/mL)	202.440 (46.111)	181.479 (39.351)	181.350 (54.063)	189.005 (42.926)	0.540 0.381 0.049	0.221 1.533 0.027	0.010[a] 7.089 0.114
MMP-9 (ng/mL)	385.156 (252.873)	368.774 (232.441)	448.613 (206.478)	414.338 (269.261)	0.223 1.521 0.029	0.421 0.657 0.013	0.936 0.007 0.000

HIT: high-intensity training group, CT: control training group; ANOVA: analysis of variance; SDMT: Symbol Digit Modalities Test; VLMT: Verbal Learning Memory Test; BVMT-R: Brief Visuospatial Memory Test–Revised; TMT A/B: Trail-Making Test; TAP: Test Battery of Attention Performance; $VO_{2\text{-peak}}$: peak oxygen uptake; BDNF: brain-derived neurotrophic factor; MMP: matrix metalloproteinase.

[a]Significant main effects (time or group) or interaction (time × group).

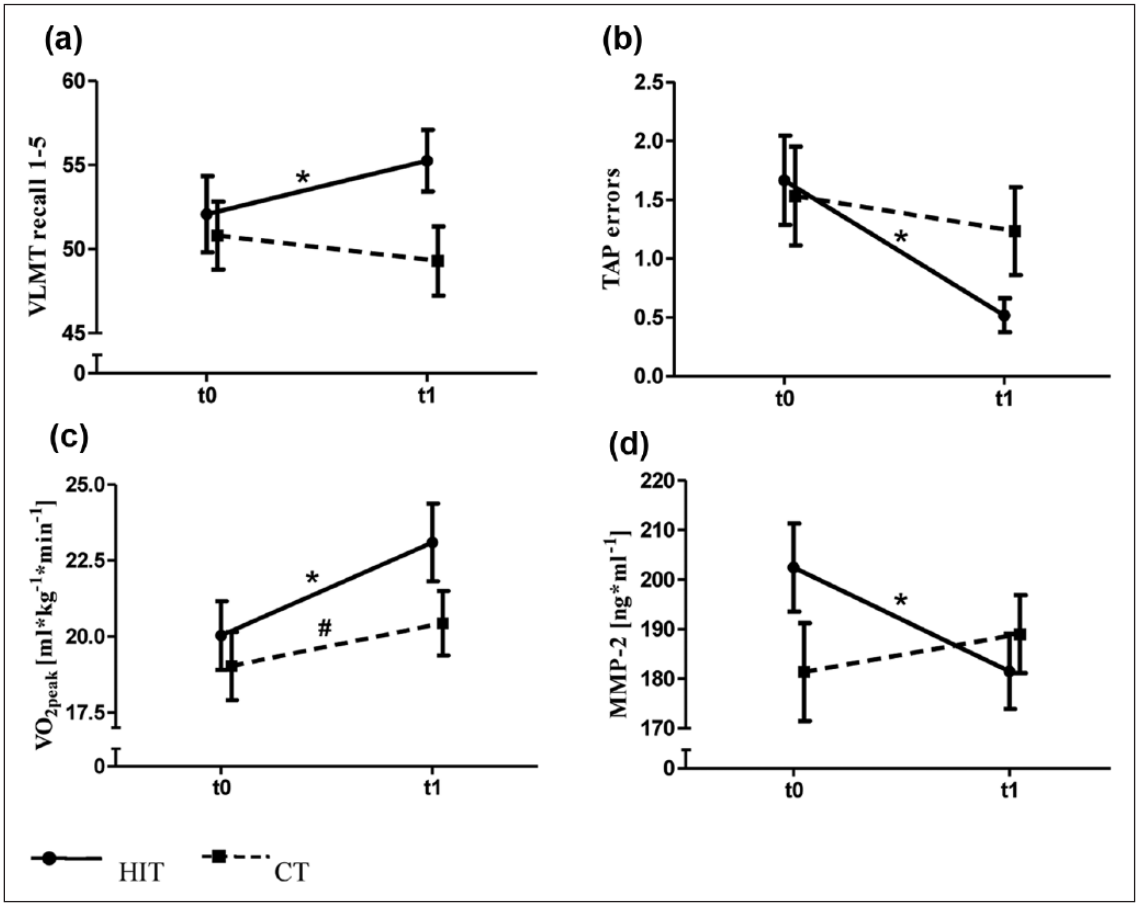

Figure 2. Simple effects analysis (SEA) for significant time*group interactions. SEA results from t_0 to t_1. (a) HIT: high-intensity training group, CT: control training group; VLMT: Verbal Learning Memory Test – higher number of recalled words indicates better performance; (b) TAP: Test Battery of Attention Performance – lower number of errors indicates better response inhibition; (c) endurance capacity – higher $VO_{2\text{-peak}}$ values indicate better cardiorespiratory fitness; (d) resting MMP-2 levels in ng/mL – higher MMP-2 serum levels are associated with disease progression; data are presented as means ± standard error of the mean. *Significant changes in HIT group; #significant changes in CT group. For exact *p* values and 95% confidence interval (95% CI) see main text.

assessments are applied. The use of different control groups further impedes the interpretation of data. Data from this investigation, using cognition as a primary endpoint and a standardized exercise regime as control group, appear to be controlling for these factors.

One pilot study has investigated the impact of high-intensity resistance training on cognitive performance in pwMS. Kierkegaard et al.[31] showed positive effects on processing speed (SDMT) after a 12-week high-intensity resistance training in pwMS. Although their results were in line with this study, learning effects may explain our findings as no time*group interactions were observed. Because Kierkegaard et al.[31] evaluated resistance training, the results are not comparable, since different physiological effects are expected following endurance exercise. Previous investigations into the effects of exercise on cognitive performance in MS have compared low- or moderate-intensity exercise with waitlist controls.

Briken et al.[32] compared the influence of different types of moderate aerobic exercise (arm crank ergometer vs rowing vs cycling) with the cognitive performance of waitlist controls. The authors reported significant improvements in verbal memory (VLMT) and attention (TAP test).The results from this study confirm those of Briken et al.[32] and extend them by showing that HIT improves verbal learning and attention compared with moderate endurance training. However, similar to the results of Briken et al.,[32] our results are limited by the lack of a clearly defined level of cognitive impairments at baseline. Sandroff et al.[3,14] reported improved verbal memory and processing speed after 12-weeks of treadmill exercise compared with waitlist controls. Conversely, Oken

et al.[15] report no effects on cognitive performance although defined as primary endpoint. As participants exercised once a week at low intensities, it is hypothesized that the intervention was too mild to induce physiological adaptations resulting in cognitive benefits.

The correlation analysis confirms previous findings on associations between cardiorespiratory fitness and cognitive performance in pwMS at baseline. However, these correlations are weak and show no significant correlations for changes in $VO_{2\text{-peak}}$ and cognitive performance.

The results of this study confirm previous research showing that HIT is efficient for increasing cardiorespiratory fitness in pwMS.[17] Other studies using HIT in pwMS focus on different endpoints showing positive effects on muscle fibre composition and function, endurance capacity and metabolic properties.[17]

Although serum levels of BDNF did not confirm any effects, data show a clear empirical increase in resting levels of serum BDNF. Conversely, other studies reported significant increases in peripheral BDNF following exercise.[33] The fact that the serum levels of BDNF do not show a time effect or time*group interaction in this study may be due to its short duration.[3]

An imbalance of MMP levels is implicated in MS; brain tissue levels of MMP-2, -7, -9 and -12 are reported to be elevated.[9] The precise mechanisms of inflammatory cell traffic through the blood–brain barrier in MS remain unknown, but MMPs have emerged as key pathogenic molecules that disrupt the blood–brain barrier.[9] Results show significant reductions in the resting serum level of MMP-2 in the HIT and confirm those of an exercise trial in pwMS by Deckx et al.[34] where MMP-9 levels remain stable. Since MMP-2 has been described to be involved in inflammatory processes, the detected negative association between changes in $VO_{2\text{-peak}}$ and serum MMP-2 levels supports the hypothesis that regular exercise has anti-inflammatory properties. This hypothesis should be addressed in future trials.

This study has some limitations. First, sample size calculation was conducted to show time*group interaction effects of $f=0.2$. To detect potential smaller effects, the study is underpowered regarding the borderline significances for cognitive outcomes (TAP errors). Second, positive effects on SDMT and TMT/B were shown for both groups. The study design is not appropriate to determine whether these effects are driven by the exercise programmes. Exercise programmes are known to be effective in rehabilitation of pwMS; the establishment of complete passive control groups remains critical from an ethical point of view. In general, the use of test batteries is recommended in clinical settings.[1,35] To get more detailed information on a specific cognitive domain, it may also be interesting to focus on specific cognitive functions in the future. This issue should also be kept in mind when performing sample size calculation, since learning effects and effects of exercise may vary between different assessments and cognitive domains.[35] A more profound view on the interaction of cognitive domains will be necessary in the future. It cannot be ruled out that general impaired processing speed in MS contributes to decreased performance in other cognitive domains.[36] Third, the overall duration of this study was comparably short. However, the 3-week intervention period was chosen as it represents a typical inpatient rehabilitative setting. Fourth, enrolling only patients with a certain level of cognitive impairments at baseline would have increased the likelihood of improvements at discharge. Fifth, a wider range of inflammatory and anti-inflammatory biomarkers, (IL-6, TNF-α and IL-10) and more measurement time points (acute and follow-up) may provide relevant information about their kinetics in response to different exercise modalities. Finally, generalizability is limited due to the inclusion criteria, comprising only patients in a supervised setting with relapsing–remitting and secondary progressive MS. However, comparisons of cognitive performance data with validation studies of the BICAMS indicate that participants of this study represent a typical MS population holding cognitive impairments compared to healthy controls.[37,38] Further research has to investigate if HIT can also be applied on a home-based basis.

In conclusion, HIT programmes are a time-efficient supportive therapy that can easily be integrated into a MS rehabilitative setting to improve the physical and cognitive constitution of these patients. Further research should investigate to what extend exercise can influence biological mechanisms which contribute to cognitive performance in the context of MS.

Acknowledgements

The authors thank Mariel Pieth, head of Viollier, Bad Ragaz AG for support in management of the blood sampling. This study was registered at ClinicalTrials.gov (NCT02571335). P.Z. and J.B. contributed equally to this work. P.Z., W.B., J.K., S.R., J.Ko., D.L. and J.B. designed the research. J.K. and J.B. obtained funding and sat on the steering committee, J.B. coordinated the study, A.S. performed analysis of biomarkers. A.S. and M.O. designed the figures. P.Z., M.O. and J.B. performed the statistical analysis. W.B., M.O., S.R., J.Ko., W.B., U.D. and D.L. supported the data

interpretation. P.Z. and J.B. drafted the paper. W.B., M.O., A.S. J.K., J.Ko., D.L., U.D. and S.R. revised and approved the manuscript.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: A.S., M.O., W.B., J.K. and J.Ko. reported no conflicts of interest, with the exception of the funding of this study through the Swiss MS Society. J.B. further reported personal fees of EXEMED for participating in a speaker board. D.L. further reported grants and personal fees from Novartis, Bayer and Biogen (research grants, consultancy, speaker bureau, conference sponsorship) and personal fees from Merck, TEVA (consultancy, speaker bureau, conference sponsorship) and Almirall, EXCEMED (speaker bureau), P.Z. further reported support from Novartis (travel grants, speaker board), Roche and Vifor Pharma (speaker board). U.D. has received travel and/or research grants from Novartis, Biogen Idec, Genzyme, Serono and TEVA.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Swiss MS Society (Grant no. 16-00093).

References

1. Langdon DW, Amato MP, Boringa J, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). *Mult Scler* 2012; 18(6): 891–898.
2. Heine M, van de Port I, Rietberg MB, et al. Exercise therapy for fatigue in multiple sclerosis. *Cochrane Database Syst Rev* 2015; 9: CD009956.
3. Sandroff BM, Motl RW, Scudder MR, et al. Systematic, evidence-based review of exercise, physical activity, and physical fitness effects on cognition in persons with multiple sclerosis. *Neuropsychol Rev* 2016; 26(3): 271–294.
4. Kalron A and Zeilig G. Efficacy of exercise intervention programs on cognition in people suffering from multiple sclerosis, stroke and Parkinson's disease: A systematic review and meta-analysis of current evidence. *Neurorehabilitation* 2015; 37(2): 273–289.
5. Baek S-S. Role of exercise on the brain. *J Exerc Rehabil* 2016; 12(5): 380–385.
6. Zimmer P, Stritt C, Bloch W, et al. The effects of different aerobic exercise intensities on serum serotonin concentrations and their association with Stroop task performance: A randomized controlled trial. *Eur J Appl Physiol* 2016; 116(10): 2025–2034.
7. Walsh NP, Gleeson M, Shephard RJ, et al. Position statement. Part one: Immune function and exercise. *Exerc Immunol Rev* 2011; 17: 6–63.
8. Bellafiore M, Battaglia G, Bianco A, et al. The involvement of MMP-2 and MMP-9 in heart exercise-related angiogenesis. *J Transl Med* 2013; 11: 283.
9. Lindberg RL, De Groot CJ, Montagne L, et al. The expression profile of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) in lesions and normal appearing white matter of multiple sclerosis. *Brain* 2001; 124(Pt 9): 1743–1753.
10. Takimoto M and Hamada T. Acute exercise increases brain region-specific expression of MCT1, MCT2, MCT4, GLUT1, and COX IV proteins. *J Appl Physiol* 2014; 116(9): 1238–1250.
11. Quistorff B, Secher NH and van Lieshout JJ. Lactate fuels the human brain during exercise. *FASEB J* 2008; 22(10): 3443–3449.
12. Erickson KI, Leckie RL and Weinstein AM. Physical activity, fitness, and gray matter volume. *Neurobiol Aging* 2014; 35(Suppl. 2): S20–S28.
13. Gomez-Pinilla F and Hillman C. The influence of exercise on cognitive abilities. *Compr Physiol* 2013; 3(1): 403–428.
14. Sandroff BM, Johnson CL and Motl RW. Exercise training effects on memory and hippocampal viscoelasticity in multiple sclerosis: A novel application of magnetic resonance elastography. *Neuroradiology* 2016; 59(1): 61–67.
15. Oken BS, Kishiyama S, Zajdel D, et al. Randomized controlled trial of yoga and exercise in multiple sclerosis. *Neurology* 2004; 62(11): 2058–2064.
16. Sandroff BM, Klaren RE, Pilutti LA, et al. Randomized controlled trial of physical activity, cognition, and walking in multiple sclerosis. *J Neurol* 2014; 261(2): 363–372.
17. Wens I, Dalgas U, Vandenabeele F, et al. High intensity exercise in multiple sclerosis: Effects on muscle contractile characteristics and exercise capacity, a randomised controlled trial. *PLoS ONE* 2015; 10(9): e0133697.
18. Wens I, Dalgas U, Vandenabeele F, et al. High intensity aerobic and resistance exercise can improve glucose tolerance in persons with multiple sclerosis: A randomized controlled trial. *Am J Phys Med Rehabil* 2017; 96(3): 161–166.
19. Ramos JS, Dalleck LC, Tjonna AE, et al. The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function:

A systematic review and meta-analysis. *Sports Med* 2015; 45(5): 679–692.

20. Sandroff BM, Pilutti LA, Benedict RHB, et al. Association between physical fitness and cognitive function in multiple sclerosis: Does disability status matter? *Neurorehabil Neural Repair* 2015; 29(3): 214–223.
21. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the 'McDonald criteria'. *Ann Neurol* 2005; 58(6): 840–846.
22. Bansi J, Bloch W, Gamper U, et al. Training in MS: Influence of two different endurance training protocols (aquatic versus overland) on cytokine and neurotrophin concentrations during three week randomized controlled trial. *Mult Scler* 2013; 19(5): 613–621.
23. Lehrl S, Triebig G and Fischer B. Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. *Acta Neurol Scand* 1995; 91(5): 335–345.
24. Herrmann-Lingen C, Buss U, Snaith RP, et al. *Hospital Anxiety and Depression Scale – Deutsche version* (3. Aktualisierte und neu normierte Auflage). Göttingen: Hogrefe, 2011.
25. Penner IK, Raselli C, Stocklin M, et al. The Fatigue Scale for Motor and Cognitive Functions (FSMC): Validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler* 2009; 15(12): 1509–1517.
26. Bowie CR and Harvey PD. Administration and interpretation of the Trail Making Test. *Nat Protoc* 2006; 1(5): 2277–2281.
27. Becker M, Sturm W, Willmes K, et al. Normierungsstudie zur Aufmerksamkeitstestbatterie (TAP) von Zimmermann, Fimm. *Z Neuropsychol* 1996; 9: 3–15.
28. Smith A. *Symbol Digit Modalities Test (SDMT) manual* (revised). Los Angeles, CA: Western Psychological Services, 1982.
29. Delis DC, Kramer JH, Kaplan E, et al. *California verbal learning test (CVLT)*. 2nd ed. San Antonio, TX: The Psychological Corporation, 2000.
30. Benedict RHB. *The brief visuospatial memory test revised (BVMT-R)*. Lutz, FL: Psychological Assessment Resources, 1997.
31. Kierkegaard M, Lundberg IE, Olsson T, et al. High-intensity resistance training in multiple sclerosis – An exploratory study of effects on immune markers in blood and cerebrospinal fluid, and on mood, fatigue, health-related quality of life, muscle strength, walking and cognition. *J Neurol Sci* 2016; 362: 251–257.
32. Briken S, Gold SM, Patra S, et al. Effects of exercise on fitness and cognition in progressive MS: A randomized, controlled pilot trial. *Mult Scler* 2014; 20(3): 382–390.
33. Wens I, Keytsman C, Deckx N, et al. Brain derived neurotrophic factor in multiple sclerosis: Effect of 24 weeks endurance and resistance training. *Eur J Neurol* 2016; 23(6): 1028–1035.
34. Deckx N, Wens I, Nuyts AH, et al. 12 Weeks of combined endurance and resistance training reduces innate markers of inflammation in a randomized controlled clinical trial in patients with multiple sclerosis. *Mediators Inflamm* 2016; 2016: 6789276.
35. Wefel JS, Vardy J, Ahles T, et al. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol* 2011; 12(7): 703–708.
36. DeLuca J, Chelune GJ, Tulsky DS, et al. Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? *J Clin Exp Neuropsychol* 2004; 26(4): 550–562.
37. Goretti B, Niccolai C, Hakiki B, et al. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS): Normative values with gender, age and education corrections in the Italian population. *BMC Neurol* 2014; 14: 171.
38. Vanotti S, Smerbeck A, Benedict RHB, et al. A new assessment tool for patients with multiple sclerosis from Spanish-speaking countries: Validation of the Brief International Cognitive Assessment for MS (BICAMS) in Argentina. *Clin Neuropsychol* 2016; 30(7): 1023–1031.