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

Running head: Exercise, cognition and multiple sclerosis

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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 three-week high-intensity aerobic exercise programme (HIT) on cognitive performance in persons with multiple sclerosis (MS) compared with a standard exercise programme (CT).

*Methods:* 60 persons with MS (EDSS 1.0-6.5) were randomized to a HIT group (3×/week à 20 minutes, including five three-minute exercise intervals at 80% of peak oxygen uptake (VO2-peak))or a CT group (continuously 5×/week for 30 minutes/session at 65% of VO2-peak).Cognitive performance was assessed using the Brief International Cognitive Assessment for MS at entry (t0) and discharge (t1). Furthermore, VO2-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 VO2-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..

This study was registered at ClinicalTrials.gov (NCT02571335).

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1 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 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.89-11 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, 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 aging 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. have shown improved cognitive function in pwMS who have participated in a theory-based program for increasing physical activity.16

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 (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 three-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.

2 MATERIAL AND METHODS

*2.1 Study design*

This RCT with blinded outcome assessment evaluated a three-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 (t0) and discharge (t1) to the three-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.

*2.2 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 eight-month period. 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.

*2.3 Randomization and masking*

Sixty 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.

*2.4 Treatments*

HIT comprised five three-minute physiologically high-intensity intervals of cycling at 80–100 revolutions per minutes (rpm) (85–90% of maximum heart rate (HRmax) or 80% of peak oxygen uptake (VO2-peak). During intervals the cadence was reduced to 50–60 rpm for 1.5 minutes to reduce heart rate to 50–60% of HRmax. 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 rpm at the lactate threshold (70% of HRmax or 65% of VO2-peak). A training session lasted 30 minutes, with warm-up and cool-down for the first and last two 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.

*2.5 Cardiopulmonary exercise testing*

All participants performed graded CPET on a cycle ergometer (Ergoline Ergoselect 200, Bitz, Germany) at entry and discharge in order to determine cardiorespiratory fitness (VO2-peak) as previously reported by Bansi et al..22

*2.6 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 Fatigue Scale for Motor and Cognitive Functions (FSMC).25

*2.7 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 t0 and t1.

*2.8 Serum levels of serotonin, BDNF, MMP2 and MMP9*

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, Minneapolis, USA) according to the manufacturer's instructions. Serum serotonin was measured by high-performance liquid chromatography (HPLC) with colorimetric detection (Agilent HP 1200, Santa Clara, CA, USA).

*2.9. Statistical analysis*

Sample size calculation was performed using G\*power software (University 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 t0 and at t1 was estimated at r=0.5. Power analysis was conducted to detect any interaction effects between within-subjects factor time-point (t0 vs. t1) 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 SD compared to healthy, age matched norm data) in at least one of the three BICAMS tests or the TMT A/B), fitness (VO2-peak), intelligence, depression, fatigue and disability levels (EDSS ) were investigated using independent *t*-tests and Fischer's exact tests. Differences 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 η2) 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).

3 RESULTS

Between 1 September 2015 and 31 May 2016 60 patients were included and 57 completed the study; 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%.

\*Figure 1.\*

Participants' characteristics are listed in Table 1. No baseline differences between groups were found. In total, 57.9 % of study participants indicated cognitive impairments.

\*Table 1.\*

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 (VO2-peak). Interaction effects (time × group), showed significant differences for verbal memory (VLMT), cardiorespiratory fitness (VO2-peak) and serum MMP-2 levels.

\*Table 2.\*

Subsequent SEA showed significant improvement of verbal memory in the HIT (*p*=0.046, 95% 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, 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 2A-D).

\*Figure 2.\*

Correlation analysis revealed significant correlations between VO2-peak and cognitive performance in some cognitive domains at t0 (SDMT: r=.292; p=.027, VLMT: r=.281; p=.034) and at t1(SDMT: r=.271; p=.042, VLMT: r=.244; p=.068, TMT A: r=-.316; p=.017, TMT B: r=-,333; p=.011, TAP errors: r=-.283; p=.033 ), whereas changes in VO2-peak showed no association with changes in cognitive performance (SDMT: r=-.149; p=.270, VLMT: r=.086; p=.526, BVMT-R: r=.074; p=.586, TMT A: r=.011; p=.938, TMT B: r=.181; p=.178, TAP time: r=.145; p=.283, TAP errors: r=-.049; p=.719). However, changes in VO2-peak indicated a negative association with serum MMP-2 levels (r=-.310; p=.019).

4 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 three-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-analysis4 report 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 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 and colleagues32 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’s 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 VO2-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 VO2-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 remain 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 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 three-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.

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AUTHOR'S CONTRIBUTIONS

PZ and JB contributed equally to this work. PZ, WB, JK, SR, JKO, DL and JB designed the research. JK and JB obtained funding and sat on the steering committee, JB coordinated the study, AS performed analysis of biomarkers. AS and MO designed the figures. PZ, MO and JB performed the statistical analysis. WB, MO, SR, JKO, WB, UD and DL supported the data interpretation. PZ and JB drafted the paper. WB, MO, AS JK, JKO, DL, UD and SR revised and approved the manuscript.

POTENTIAL CONFLICT OF INTERESTS

AS, MO, WB, JK, JKO and reported no conflicts of interest, with the exception of the funding of this study through the Swiss MS Society. JB further reported personal fees of EXEMED for participating in a speaker board. DL 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), PZ further reported support from Novartis (travel grants, speaker board), Roche and Vifor Pharma (speaker board). UD has received travel and/or research grants from Novarrtis, Biogen Idec, Genzyme, Serono and Teva.

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FIGURE LEGENDS

**Figure 1. Trial profile.**

**Figure 2. Simple effects analysis (SEA) for significant time \* group interactions.**

SEA results from t0 to t1. HIT: high-intensity training group, CT: control training group; VLMT: Verbal Learning Memory Test – higher number of recalled words indicates better performance (a); TAP: test battery of attention performance – lower number of errors indicates better response inhibition (b); endurance capacity – higher VO2-peak values indicate better cardiorespiratory fitness (c); resting MMP-2 levels in ng/ml – higher MMP-2 serum levels are associated with disease progression (d); 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.