

Benefits of Individualized Training in Fatigued Patients with Multiple Sclerosis

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ABSTRACT

ROYER, N., J. MIRA, N. LEPETIT, E. FAYOLLE, J.-P. CAMDESSANCHÉ, and G. Y. MILLET. Benefits of Individualized Training in Fatigued Patients with Multiple Sclerosis. *Med. Sci. Sports Exerc.*, Vol. 56, No. 9, pp. 1623–1633, 2024. **Introduction:** Chronic fatigue is the most common and debilitating symptom in people with multiple sclerosis (PwMS). Recently, exercise has been proven to alleviate chronic fatigue and improve physical functions. Tailoring the training intervention to the potential fatigue causes could optimize the beneficial effects of training on fatigue. The objective of this study was to compare the effectiveness of an individualized (IND) versus a traditional (TRAD) exercise intervention in reducing chronic fatigue. **Methods:** Twenty-nine PwMS with high chronic fatigue were randomly assigned to 12 wk of either a TRAD or IND exercise intervention. TRAD comprised aerobic and resistance exercises according to the guidelines for PwMS. IND specifically addressed identified individual weaknesses. Participants visited the laboratory before and after training for the following assessments: patient-reported outcomes (fatigue, quality of life, depression questionnaires), incremental cycling test (peak oxygen uptake ($\dot{V}O_{2\text{peak}}$)), and cycling fatigue test (maximal voluntary contraction, rating of perceived exertion). **Results:** Similar improvements in fatigue, depression, and quality of life were observed between groups ($P > 0.05$). Compared with TRAD, IND induced a significant greater increase in $\dot{V}O_{2\text{peak}}$ ($+21.0\% \pm 13.9\%$ vs $6.8\% \pm 11.5\%$, $P < 0.05$) and a greater reduction in rating of perceived exertion at a given submaximal intensity ($-30.3\% \pm 18.9\%$ vs $-12.1\% \pm 20.4\%$, $P < 0.001$), whereas maximal voluntary contraction increased similarly in both groups ($P > 0.05$). **Conclusions:** Although tailored exercise improved similarly fatigue and other subjective parameters (depression, quality of life, sleep quality) compared with than traditional exercise intervention, prescribing an individualized intervention led to greater improvement in $\dot{V}O_{2\text{peak}}$ (but not maximal strength) and perception of effort. This may have positive functional consequences for patients. **Key Words:** INDIVIDUALIZED TRAINING, MULTIPLE SCLEROSIS, EXERCISE, SUBJECTIVE PARAMETERS, OBJECTIVE PARAMETERS

Multiple sclerosis (MS)-related fatigue is one of the most disabling symptoms, and it is experienced by 80% of people with MS (PwMS) across all disability levels (1). Fatigue has been defined as a “subjective lack of physical and/or mental energy, perceived by the individual or caregiver to interfere with usual and desired activities” (2). Despite the high prevalence of fatigue, its pathophysiology is poorly understood. It likely involves primary mechanisms

such as inflammation, gray and white matter lesions, and functional disconnections, as well as secondary mechanisms such as disrupted sleep, mood disorders, physical inactivity, and sometimes the side effects of medication (3). The MS-related fatigue has primarily been assessed using self-reported questionnaires such as the Fatigue Severity Scale (FSS) or the Modified Fatigue Impact Scale (MFIS) (4). However, surveys measure only the subjective aspects of fatigue (or perceived fatigue), and it is important to also consider objective fatigue (or fatigability). Fatigability is defined as the magnitude or rate of decrease in force or power due to exercise (5). In fact, an exacerbated fatigability, measured by a greater decline of maximal voluntary contraction (MVC) force after dynamic whole-body exercise, was found in fatigued compared with non-fatigued PwMS and/or control subjects (6,7). This greater fatigability in PwMS could lead to a greater reduction in functional capacity, and over time, the repetition of the activity of daily living could induce fatigue accumulation. This fatigue accumulation may lead PwMS to do less exercise during the day, which could induce deconditioning and in turn enhance chronic fatigue in a vicious circle (8).

The recent pharmacological treatment advances have reduced the number of relapses and their severity but symptoms such as

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MS-related fatigue, muscle weakness, physical deconditioning, and balance disorders are not specifically improved by disease-modifying drugs (9). PwMS have been advised for a long time to reduce their physical activity and adapt their lifestyle because exercise was considered as a factor increasing the MS symptoms (10). At present, PwMS are less physically active than healthy people (11). This has been a major contributor to patients deconditioning, as shown by the association between greater sedentary time and inactivity with lower walking performance (12), fatigue (13), and high blood pressure (14). In addition, patients with greater fatigability were those with the greatest perceived fatigue (6,7). Recommendations to reduce inactivity have been recently proposed throughout physical activity guidelines (15). These guidelines propose various approaches to perform exercise, for example, resistance and endurance training, water exercises, stretching, or physiotherapy sessions.

Numerous studies have recently shown the benefits of exercise interventions among PwMS (16). Strength training, aerobic training, or combined training appears to be effective in reducing subjective fatigue, as highlighted by meta-analyses (17–19). More precisely, from the analysis of 31 articles, a 36% reduction in the standardized mean difference for the fatigue score was observed following an exercise intervention (18). Moreover, according to the type of exercise, other improvements have been reported on physical capacities such as muscle strength, cardiorespiratory capacity, walking speed, balance, and cognition (20). Exercise training can also improve sleep disorders, depressive feelings, and other psychological aspects (20). However, there is a great heterogeneity in the methods in terms of type, frequency, or intensity of exercise (21). In addition, the effects of exercise may vary between PwMS, as MS is an heterogeneous disease and does not affect each individual in the same way (22). A meta-analysis conducted on the effects of exercise in cancer patients showed that the reduction in perceived fatigue was greater when exercise was adapted to the symptoms (23). Moreover, the authors suggested that exercise interventions need to be tailored to medical outcomes. Recently, Twomey et al. (24) proposed a tailored exercise approach based on physiological outcomes to improve cancer-related fatigue. By specifically addressing the causes of fatigue, the exercise intervention, it was hypothesized that fatigue would be reduced more. Specific examples are proposed in the methods section (see “Individualized exercise group (IND)”). Some training programs have recently tailored interventions with PwMS to improve the effects of exercise interventions (25–27). Although no study investigated the tailored exercise approach to specifically alleviate fatigue of MS patients, targeting physical capacities with this type of training can lead to reduction of fatigue in PwMS. For instance, Mayo et al. (25) compared the effectiveness of a 1-yr tailored exercise program (where exercises were built according to the physical/psychological status of each patient) to an intervention that followed exercise guidelines for PwMS. The individualized program included high-intensity interval training (HIIT) and low-intensity aerobic exercise, strength training, and stretching.

The authors observed that the positive effects on fatigue were greater after the individualized intervention compared with the intervention following guidelines, but the cardiorespiratory fitness level was not changed in either group. Moreover, Bouquiaux et al. (26) used an individualized training circuit with 12 exercises such as walking, muscle strengthening, and balance adapted to patients’ capacities. Although the depression and fatigue were not modified by the intervention, walking tests, quality of life, cardiorespiratory capacity, and physical fitness were significantly improved, yet this study was not a randomized controlled trial. To the best of our knowledge, although these recent studies have tried to target the most important physical abilities with training, no experiment has ever designed a training intervention based on the profile of each patient. Here, we designed a protocol specifically individualized to the patient’s weaknesses (e.g., low muscle strength, reduced cardiorespiratory fitness, sleep disturbances), based on a multifactorial assessment performed at baseline. Thus, this project aimed to determine the benefits of a tailored exercise intervention compared with a traditional exercise intervention in improving fatigue as primary outcome and other variables such as quality of life, depression, cardiorespiratory fitness, force, and fatigability as secondary outcomes. We hypothesized that tailored exercise intervention would be more effective than traditional exercise to reduce subjective fatigue and increase quality of life among fatigued PwMS. Moreover, it was hypothesized that there would be a greater improvement of objective (e.g., cardiorespiratory fitness, MVC, fatigability) and subjective (e.g., depression, quality of life) measurements after tailored exercise intervention compared with a traditional exercise intervention.

MATERIALS AND METHODS

Participants

Twenty-nine fatigued PwMS with relapsing-remitting MS (RRMS) were recruited, following the inclusion and exclusion criteria presented in Table 1. Only patients who have obtained a score of ≥ 4 on the FSS questionnaire and a score of ≥ 38 on the MFIS were included. Upon arrival at the first session, participants were informed of the experimental protocol and of all associated risks before giving written informed consent. All study procedures were approved by a national ethic committee (Comité de Protection des Personnes Sud-Est I, Study ID 2020-A00841-38, Ethics Committee Agreement No. 20.03.31.35317).

Experimental Setup

The participants attended one testing session before the 12-wk exercise intervention, and a second one after. Participants were instructed to refrain from vigorous physical activity in the 24 h before testing and avoid caffeine ingestion 12 h before each session. The first session included the following: a health screening, the completion of questionnaires, blood sample withdrawal, MVCs on an isometric ergometer, cycling fatigue task, and an incremental cycling test. The total

TABLE 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Age 18–65 yr • Duration of disease between 2 and 25 yr • EDSS ≤ 5 • Definite RRMS • Strength (MRC grade) ≥ 4 in all leg muscles • Ability to walk 10 min without stopping (self-reported) • Ability to understand study requirements • Able to visit the laboratory on 2 different occasions >1 wk apart • Affiliated or beneficiaries of a social security system 	<ul style="list-style-type: none"> • Severe spasticity or cerebellar ataxia in either leg • Abnormal toe and/or ankle range of motion • A musculoskeletal injury which impairs cycling • Positive PAR-Q+ or an elevated resting heart rate (>90 bpm) • Blood pressure $>144/94$ mm Hg • Do not meet TMS screening questionnaire • Onset of MS relapse within 90 d of screening • Recent adjustment of any medications or medications that may impact fatigue, or taking stimulants for fatigue (e.g., modafinil, amantadine) • Subject has a history of comorbid illness or conditions that would compromise the safety of the subject during the study • Evidence (clinical or lab) of a lower motor neuron process • Current participation in another clinical investigation of a medical device or a drug; or has participated in such a study within 30 d before this study • Pregnant and nursing women • Patient incapable of understanding the purpose and conditions of the study, incapable of giving consent • Patient deprived of liberty or patient under guardianship

duration of testing sessions was about 2 h. Given the number of exercises, sufficient recovery time was planned between efforts to limit fatigue accumulation. The post-training session encompassed the same procedures, except for the health screening. After each testing session, activity level and sleep quality were assessed over a period of 7 d. Participants were randomly assigned to one of the exercise interventions using the REDcap software (28). Sample size was calculated using G*Power (version 3.1.9.7; Kiel University, Kiel, Germany), based on an expected “high” effect size ($f^2 = 1.12$) for a difference of 0.45 (± 0.40) (29,30) in FSS changes at post-training between the two training types with α level of 0.05 and power ($1 - \beta$) of 0.8.

Procedures

Questionnaires. Subjective fatigue was measured using the FSS and the MFIS, which evaluate fatigue over the previous week and the previous month, respectively. The MFIS includes both a physical, psychosocial and mental component, whereas the FSS is primarily related to physical component of fatigue. Then, different questionnaires were completed: The French Multiple Sclerosis Quality of Life (SEP-59) to evaluate quality of life (31), the Center for Epidemiologic Studies Depression Scale (CES-D) for the depression (32), and the Pittsburgh Sleep Quality Index (PSQ-I) for the sleep quality (33). Physical activity levels (duration and intensity over the previous month) were assessed using Godin Leisure Time Exercise Questionnaire (34) and actigraphy (see discussion hereinafter).

Blood sample. A blood sample (12 mL) was collected from the antecubital fossa by a nurse or physician between 9:30 and 10:30 AM. C-reactive protein (CRP) concentration was measured, and a complete blood count was performed. Blood samples allowed the evaluation of potential anemia and inflammation, two major potential causes of the sensation of chronic fatigue (35,36).

Voluntary isometric force measurement. Participants sat on an isometric dynamometer (ARS dynamometry; SP2, Ltd., Ljubljana, Slovenia) with the hip and the right knee at 70° flexion (full hip and knee extension = 0°). Knee extensors and pelvis were strapped to avoid any undesirable movements.

The force signal was recorded at a sampling frequency of 2 kHz using a PowerLab System (16/30; ADInstruments, Bella Vista, Australia) and LabChart 8 software (ADInstruments). After a short warm-up, MVC was performed on the isometric dynamometer. During maximum force measurements, patients were instructed to contract as hard as possible, and were verbally encouraged by the experimenter. Two contractions on each leg were performed between PwMS.

Fatiguing and cardiopulmonary exercise testing. The fatiguing dynamic exercise was performed on the innovative cycling ergometer designed by the laboratory (see Supplemental Fig. 1, Supplemental Digital Content, Overview of the innovative cycle-ergometer and the protocol during laboratory visit, <http://links.lww.com/MSS/D37>) using a scientifically validated instrumented measuring pedal (PowerForce pedal, Model PF1.0.0; Radlabor GmbH, Freiburg, Germany) (37). This ergometer allows the pedals to lock instantaneously with the right knee at a 90° angle to assess isometric force and fatigability of the knee extensors immediately following cycling exercise. When measuring force, hip angle was approximately 100° and the knee and ankle angles were approximately 90°. The use of two belts attached to the thorax minimized upper body movements. The cycling fatiguing exercise comprised two stages of 3 min each. The first stage was performed at 0.3 W·kg⁻¹ of bodyweight and then power output was increased to 0.6 W·kg⁻¹ for the second stage. Before stage 1, in-between stages, and immediately after stage 2, the following neuromuscular evaluation was carried out: 5-s isometric MVC of the right knee extensors with a superimposed twitch, and a potentiated twitch on the relaxed muscle.

After the last neuromuscular evaluation, participants benefited from a 5-min rest period. To measure aerobic capacity, subjects then completed an incremental test using breath-by-breath portable analyzer (Metamax 3B-R2; Cortex Medical, Leipzig, Germany). The cycling protocol began at 25 W and increased by 10, 15, or 20 W every minute until volitional exhaustion. The protocol was predetermined based on each individual's activity level, and health and fitness status in order to reach failure in ~8–12 min (volitional exhaustion or unable to maintain the cadence) (38). Heart rate was continuously monitored using a Polar heart rate monitor (Polar H7; Polar, Kempele,

Finland). Peak oxygen uptake ($\dot{V}O_{2peak}$) was calculated from the highest 15-s average of $\dot{V}O_2$. The maximal power output (P_{max}) was measured from the highest value of power during the cycling protocol. Maximal heart rate was calculated from the maximal value obtained during the test. The first ventilatory threshold was determined with the increase of the ventilatory (\dot{V}_E), production of carbon dioxide ($\dot{V}CO_2$), partial pressure of end tidal O_2 (P_{ETO_2}), and ratio of $\dot{V}_E/\dot{V}O_2$. The second ventilatory threshold was identified from the nonlinear increase of \dot{V}_E , P_{ETO_2} , increase of $\dot{V}_E/\dot{V}CO_2$, and decrease of P_{ETCO_2} .

Sleep Evaluation and Actigraphy. Upon termination of the first session, participants were given an Actigraph (Motionwatch®, Camntech, UK) for the noninvasive measurement of sleep and sleep-wake cycles. Participants received instructions and were asked to wear the device on their nondominant wrist for the 7 d after the testing session. During this period, participants were asked to complete a sleep diary each morning. The unit of measure to evaluate physical activity was the count. Four thresholds were used for all study participants (sedentary: 178 counts per minute, light: 179–561 counts per minute, moderate: 562–1019 counts per minute, and vigorous: >1020 counts per minute) (39).

Exercise Interventions

The two training groups started the training program 1 wk after the initial visit. Subjects performed exercise 3 times a week for 12 wk supervised by a coach. The sessions lasted 60 min, warm-up and cool-down included. Stretching of the lower body was performed during the cool down for both groups. These two groups were matched for sex, age, and physical activity level measured by the actigraph.

Traditional exercise group (TRAD). The traditional exercise (TRAD) group was engaged in exercise of a duration, frequency, and intensity that is consistent with published recommendations and clinical practice guidelines for the PwMS (40). The goal of the intervention was to progress to meet guidelines of 30 min of moderate-intensity aerobic activity two times per week, and resistance training at least 2 d·wk⁻¹ for a total of 36 training sessions (see Supplemental Table 1, Supplemental Digital Content, Example of a typical week from a traditional exercise group, <http://links.lww.com/MSS/D37>). The intensity used for the exercise was based on each participant's progression to maintain a moderate intensity based on the clinical exercise guidelines for PwMS (15,40).

Individualized exercise group (IND). The first level of individualization was the type of training performed. Subjects

in the individualized exercise (IND) group were prescribed an intervention designed specifically to address the deficits or areas for improvement identified in the initial laboratory visit. The results of an individual's assessment were reviewed and discussed by the research team and exercise specialists to optimize the intervention (see Supplemental Table 2, Supplemental Digital Content 3, Distribution of exercise type for each PwMS from individualized group, <http://links.lww.com/MSS/D3>).

The intervention could be multimodal, that is, involve a combination of the following examples: if muscular strength was low (force-generating capacity in the knee extensors), the exercise intervention was focused on improving muscular strength using resistance training with voluntary contractions (see Supplemental Table 3, Supplemental Digital Content, Strength exercise used for both intervention groups, <http://links.lww.com/MSS/D37>). If a low cardiorespiratory capacity was measured, primarily based on a low $\dot{V}O_{2max}$ according to age-group norms (38), participants were prescribed two sessions of interval training per week (see Supplemental Table 4, Supplemental Digital Content, High-intensity interval training exercise used for the individualized group, <http://links.lww.com/MSS/D37>). Based on substantial sleep disturbance determined via actigraphy, there was a focus on exercise to improve sleep, that is, low-intensity aerobic exercise such as walking, performed late afternoon/early evening (41,42).

The second level of individualization was performed on the intensity of exercise. After 4 and 8 wk, the intensity was adapted according to the FSS and Rating of Fatigue Scale (ROF). Given that MS-related fatigue is one of the most common symptoms, exercise intensity was adjusted to the score obtained with the fatigue questionnaires. If the ROF was greater than or equal to 7 at the beginning of the session, the intensity of the session was halved. For a score lower than 7, the intensity was maintained. If FSS decreased from a clinical point of view (i.e., at least 15% of the initial score according to Rooney et al. (30)), the intensity of the sessions was increased by additional weights during strength sessions or a higher resistance on ergocycle during aerobic exercise sessions. If the FSS increased by 15% or more, the intensity of the session was reduced. If one of these conditions was not met, the intensity was maintained (Fig. 1).

Equipment and Measurements

Electromyography. Surface electromyographic (EMG) signals were collected continuously from electrodes (Meditrace 100; Covidien, Mansfield, MA) positioned in bipolar configuration

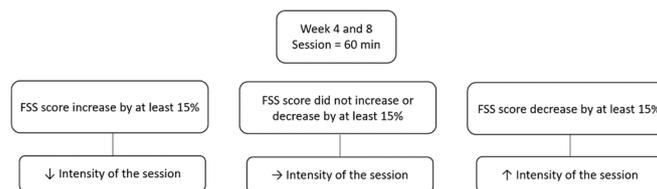


FIGURE 1—Schematic diagram representing the modulation of session intensity for the IND group. This represents the second level of individualization, the first one being the type of training performed (based on initial evaluation).

(interelectrode interval: 30 mm). The EMG signals were amplified (ML138, ADInstruments; gain = 500), filtered (bandwidth: 5–500 Hz), and sampled at a frequency of 2000 Hz (PowerLab system, 16/30-ML880/P; ADInstruments, Bella Vista, Australia). Before electrode placement, the skin was prepared, that is, shaved, sanded, and cleaned with a sodium chloride solution, to promote signal collection. The reference electrode was placed on the patella. The EMG electrodes were placed on the distal part of the vastus lateralis muscle.

Peripheral nerve electrical stimulation. Twitch responses and M waves were elicited in the knee extensors. Single supramaximal stimulus was delivered with a high-voltage constant-current stimulator (modified DS7R; Digitimer, Welwyn Garden City, UK) to the right femoral nerve via a stimulating cathode electrode (Ag-AgCl discs, 20-mm diameter, Kendall MediTrace foam electrodes, Mansfield, MA) taped to the skin onto the inguinal triangle and an anode electrode 50 × 90 mm (Durastick Plus; DJO Global, Vista, CA) between the greater trochanter and gluteal fold. Supramaximal stimulus intensity was determined in the isometric chair. Electrical stimuli were delivered at 30 mA, and a ramp of electrical nerve stimulation of 10-mA increments was evoked until the resting Mmax and twitch responses plateaued. The intensity was then increased by 30% to ensure supramaximality.

Rating of perceived exertion. To determine subjective perception of effort, rating of perceived exertion (RPE) was obtained using the Borg's scale (6–20) (43). RPE was recorded in the last minute of each stage during the cycling test. The RPE was evaluated in the 3 days which followed each session to examine residual effects of physical activity.

Rating of Fatigue Scale. To monitor fatigue through the sessions during the exercise intervention, the ROF (0–10), recently validated in French by our group (44), was used. The ROF was measured at the beginning and at the end of each training session.

Neuromuscular data analysis. For the isometric chair, the highest MVC of each leg was considered. For the MVC during the cycling fatiguing task, the highest peak before PNS was considered. Maximal voluntary activation using peripheral nerve stimulation (VA_{PNS}) was measured using the twitch interpolation technique by comparing the amplitude of the superimposed twitch force to the potentiated twitch (PT) evoked at rest 2 s after the MVC. If the electrical stimulation was not delivered at peak torque, Strojnik and Komi (45) correction was used with the following equation:

$$VA_{PNS} = \left[1 - \frac{(\text{superimposed twitch force} \times (\text{force at stimulation/MVC}))}{PT \text{ force}} \right] \times 100$$

Mmax was quantified as peak-to-peak amplitude of the vastus lateralis.

Statistical Analysis

Analyses were performed with R (R Core Team (2018)) and Jamovi software (<https://www.jamovi.org/download.html>). For all tests, significance level was set at $P < 0.05$.

Data are presented as mean ± SD values. Mixed linear effects analysis was performed to determine the relationship

between subjective/objectives measurements, pre/post-test training, and groups using *lme4* package (46). As fixed effects, groups and time (with interaction term) were entered into the model. As random effects, we had intercepts for subjects. Visual inspection of residual plots did not reveal any obvious deviations from homoscedasticity or normality. P values were obtained by likelihood ratio tests of the full model with the effect in question against the model without the effect in question. Model selection was done using Akaike's Information Criterion (AIC) (47), first including all interested fixed effects and selecting random effects, and finally comparing different versions of fixed effects.

The best-fitting distribution was identified using AIC (47). Pairwise within-group comparisons between groups at different time points for each objective and subjective variable were performed using *emmeans* package (48). The P value adjusted was performed using Bonferonni test between the means of groups.

RESULTS

Training Intervention

Most of the subjects completed the 12 wk of training with high adherence (96% of the sessions were performed). Only four patients stopped the training program (injury or time constraints), representing a dropout of 14%. Three participants were excluded in each group for actigraphy data analysis because of inconsistent use of the device. Participants' characteristics are shown in Table 2. Average RPE along the 12 wk was greater for the IND group compared with the TRAD group (4.4 ± 0.7 vs 3.0 ± 0.4 , $P < 0.05$; see Supplemental Fig. 2, Supplemental Digital Content, Total RPE of the three sessions per week performed by the two interventions groups, <http://links.lww.com/MSS/D37>). AIC scores indicated that the models with training group and time without RPE group intercept random effects were the best. The ROFs were not different between groups either before (2.4 ± 1.2 vs 2.9 ± 1.7 , $P > 0.05$) or after (2.5 ± 1.3 vs 3.0 ± 1.7 , $P > 0.05$) each training session.

Subjective Measurements

The fatigue (MFIS and FSS), and physical and mental component of quality of life (SEP59) improved similarly between the two training interventions just as subjective sleep and PSQI score (Fig. 2). However, the CES-D score was reduced ($P < 0.001$) after the IND ($-41.0\% \pm 23.4\%$, $dz = 2.2$) and

TABLE 2. Characteristics of the PwMS performing traditional (TRAD) and individualized (IND) training intervention (mean ± SD).

	TRAD (n = 13)	IND (n = 12)	P
Age (yr)	48.2 ± 9.2	52.0 ± 9.2	0.30
Height (cm)	168.2 ± 8.4	163.6 ± 6.3	0.09
Body mass (kg)	73.4 ± 18.9	67.3 ± 14.9	0.39
Men/Women	5/8	3/9	
EDSS	2.0 ± 1.5	2.4 ± 1.7	0.66
Disease duration (yr)	10.2 ± 5.9	11.3 ± 5.0	0.62
Physical activity			
Vigorous (s)	8452 ± 3708	8580 ± 3410	0.94
Moderate (s)	9344 ± 2096	9681 ± 2660	0.76
Low (s)	13,749 ± 1760	11,693 ± 2465	0.05

EDSS, Expanded Disability Status Scale.

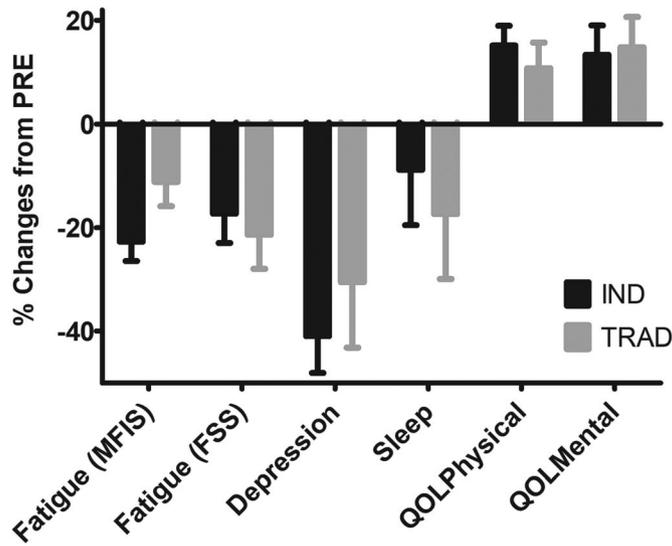


FIGURE 2—Differences between pretraining and posttraining in fatigue, depression, sleep, and quality of life (QoL) for the individualized (IND) or traditional (TRAD) training group. Statistical analyses are presented in Table 3.

the TRAD training ($-30.5\% \pm 45.4\%$, $dz = 1.1$), and there was a group–time interaction (Fig. 2).

Objective Measurements

Cardiorespiratory responses. IND induced an increase in $\dot{V}O_{2peak}$ ($+21.0\% \pm 13.9\%$, $dz = 1.5$, $P < 0.001$), whereas no differences were observed after the intervention for TRAD ($+6.8\% \pm 11.5\%$, $dz = 0.5$, $P = 0.14$). Similarly, an improvement in P_{max} was observed for IND ($19.4\% \pm 11.8\%$, $dz = 2.6$, $P < 0.001$) but not for TRAD ($3.4\% \pm 6.6\%$, $dz = 0.5$, $P = 0.4$; Fig. 3). A time effect was found for the second ventilatory threshold with an increase in both groups ($P < 0.05$), with no time–groups interaction. No significant changes due to the interventions were found for heart rate and the first ventilatory thresholds relative to pre-training (Table 3).

Neuromuscular function at rest and fatigability. After training, only a time effect was found for the MVC of the

right and the left legs ($P < 0.05$), without any time–group interaction ($P = 0.383$ and $P = 0.337$ for right and the left legs, respectively). No time effects were found for VA and peak twitch at baseline ($P > 0.05$). No significant time effects or interactions were displayed for the MVC, VA, and twitch changes after 6 and 12 min of cycling (Table 3). However, RPE at the second stage of cycling was more reduced after the IND compared with TRAD training ($-30.3\% \pm 18.9\%$ ($dz = 2.1$) vs $-12.1\% \pm 20.4\%$ ($dz = 0.8$), $P < 0.001$).

Sleep and physical activity. Sleep parameters such as fraction index ($+0.4\% \pm 1.9\%$ vs $2.8\% \pm 1.2\%$), or physical activity parameters (sedentary, light moderate, and vigorous intensity) were not changed with the IND and TRAD interventions ($P > 0.05$). Surprisingly, there was a time effect ($P < 0.05$) with a decrease in sleep efficiency, total sleep, and increase of wake time after the training interventions, but no differences were observed between IND and TRAD ($P > 0.05$).

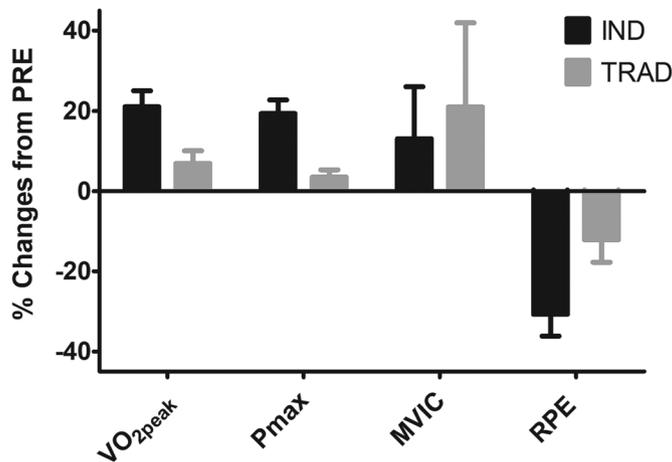


FIGURE 3—Differences between pretraining and posttraining in $\dot{V}O_{2peak}$, P_{max} , MVIC of the right leg, and RPE for the individualized (IND) or traditional (TRA) training group. Statistical analyses are presented in Table 3.

TABLE 3. Changes in objective and subjective parameters after the two training interventions.

	IND		TRAD	
	PRE	POST	PRE	POST
FSS	4.8 ± 1.3	3.8 ± 0.8*	4.7 ± 0.8	3.7 ± 1.2*
MFIS	55.4 ± 10.1	43.8 ± 7.5*	50.6 ± 15.5	43.5 ± 12.2*
CES-D	20.0 ± 9.2	12.5 ± 8.9*	13.8 ± 11.0	10.0 ± 10.3*
PSQI	9.2 ± 3.6	8.1 ± 3.8*	7.2 ± 4.2	5.7 ± 3.7*
SEP59Phy	57.7 ± 12.6	65.1 ± 9.5*	59.4 ± 10.9	64.3 ± 7.1*
SEP59Men	63.8 ± 14.3	70.8 ± 14.8*	64.8 ± 18.1	71.9 ± 13.8*
$\dot{V}O_{2peak}$ (mL $O_2 \cdot min^{-1} \cdot kg^{-1}$)	23.3 ± 6.4	27.7 ± 5.6***	26.8 ± 8.7	28.2 ± 8.3
P_{max} (W)	109 ± 34.2	128 ± 32.5***	140.0 ± 58.2	144.0 ± 59.2
HRmax (bpm)	155.0 ± 18.5	156.0 ± 18.4	146.0 ± 21.4	149.0 ± 22.1
VT1 (mL $O_2 \cdot min^{-1}$)	847 ± 239	919 ± 180	945 ± 271	981 ± 268
VT1 (% $\dot{V}O_{2peak}$)	49.3 ± 9.3	44.5 ± 5.7	43.1 ± 9.0	44.2 ± 10.0
VT2 (mL $O_2 \cdot min^{-1}$)	1247 ± 369	1403 ± 305*	1625 ± 607	1664 ± 651*
VT2 (% $\dot{V}O_{2peak}$)	71.8 ± 7.4	67.3 ± 4.8	71.6 ± 10.9	71.9 ± 9.4
MVC right (N·m)	153.0 ± 56.9	167.0 ± 51.9*	173.0 ± 68.1	199 ± 74.3*
MVC left (N·m)	155.0 ± 55.7	171.0 ± 51.3*	171.0 ± 92.6	195 ± 95.3*
RPE	12.7 ± 2.2	8.8 ± 2.6***	11.5 ± 2.8	9.8 ± 2.5*
Torque loss (% from PRE)	-17.1 ± 15.1	-13.0 ± 7.0	-13.6 ± 15.0	-16.2 ± 16.6

*Significantly different from PRE ($P < 0.05$).

**Significantly different from TRAD at POST ($P < 0.05$).

HRmax, maximal heart rate; SEP59Ment, mental component of Multiple Sclerosis Quality of Life scale; SEP59Phys, physical component of Multiple Sclerosis Quality of Life scale; Torque loss, reduction of MVC after the second stage of the cycling test; VT1, first ventilatory thresholds; VT2, second ventilatory thresholds.

Inflammatory markers. White blood cells, hematocrit, and CRP were not significantly different between pre-training and post-training interventions ($P > 0.05$).

DISCUSSION

The aim of the present study was to compare the benefits of a tailored exercise intervention to a traditional exercise intervention in improving subjective fatigue and objective parameters in highly fatigued PwMS. Contrary to our main hypothesis, tailored training was not superior to following guidelines in improving fatigue. Similarly, it did not lead to greater gains in maximal strength and fatigability, or in depression and quality of life. However, greater improvements in $\dot{V}O_{2peak}$, P_{max} , and RPE was observed when prescribing an individualized training.

Subjective Parameters

Fatigue. It was hypothesized that the IND group would induce a greater reduction in fatigue compared with TRAD. In the present study, fatigue decreased similarly after the two interventions. Given the prevalence of fatigue among PwMS, this is the most investigated subjective measure after an exercise intervention (49). Exercise (endurance, resistance, or combined training) is considered to be effective to reduce fatigue (17). Recently, Rooney et al. (30) estimated the minimal clinical important difference of FSS (0.45 points) and MFIS (4 points) score to establish a threshold value of fatigue score changes. Interestingly, both interventions caused a fatigue score decline above these minimal important differences, suggesting the efficacy of the two-training used in this study. The effects of individualized training on fatigue have been found to be contradictory. Following the exercise intervention, no change (26), similar (27), or greater improvement in fatigue was reported for the IND group compared with the TRAD group (25). Mayo et al. (25) showed that fatigue improvements were greater following a combined training (HIIT, resistance training, and other

complementary activity) than after a program based on general exercise guidelines. However, in addition to a greater intensity, the amount of training differed between the two groups in this study (6 vs 4 sessions per week). In the present study, differences were observed in terms of volume between intervention groups (see Supplemental Table 5, Supplemental Digital Content, Volume of exercise classified by type between intervention groups, <http://links.lww.com/MSS/D37>), yet it is important to note that patients of both groups spent the same amount of time in the gym per session and performed the same number of sessions per week. We can speculate that the combined training volume was higher than the volume from the control group in the study of Mayo et al. (25), which explains the difference in fatigue changes compared with our results.

Quality of life. As observed with fatigue, the physical and mental components of quality of life were improved similarly after the two training interventions. The rise of physical activity would be sufficient to have some benefits on quality of life through social support, disability, fatigue, mood, pain, and self-efficacy (50). Recently, the combination of HIIT and resistance training induced improvements of specific components of the SEP-59 (vitality, general well-being, and physical subscore) (51). It has been demonstrated that individualized training produced greater progress for the mental components of the quality of life (26) although this is not a consistent result (25). However, they did not include a control group to compare their results with the IND group. We can speculate that the improvement in quality of life was limited by the similar changes in fatigue and depression after the two training interventions. A recent meta-analysis observed that improvements in quality of life with exercise are significant but low (52). The IND training could likely not be effective enough compared with other TRAD to produce distinct modifications of the quality of life.

Depression. In our study, the depression score was reduced similarly between the two groups ($-41.0\% \pm 23.4\%$ vs $-30.5\% \pm 45.4\%$). A meta-analysis investigating the effect

of exercise on depression, including resistance or endurance training performed separately, showed that depressive symptoms could be reduced or prevented among PwMS with exercise (53). Regarding the combined training, the results are more contrasted, as no improvements have been observed in the past (54). Importantly, both interventions were able to produce a reduction in depression score despite the low level of depression of PwMS. Recently, a tendency toward a reduction in depression ($P = 0.07$) was observed after 18 wk of individualized training. In contrast to what has been performed in this study, we managed the intensity of the sessions throughout the week with respect to the progression of each PwMS from the IND group, which may explain the differences observed with their findings. Moreover, contrary to Bouquiaux et al. (26), who have set up autonomous sessions, all sessions were supervised, which is important considering the role of supervision on the psychological effects of exercise intervention.

RPE. The high perception of effort is a major component of fatigue among PwMS (55). RPE at the second stage of cycling was decreased to a greater extent for the IND group compared with the TRAD group. In a more nominal way, IND moved from “somewhat hard (13)” to “very light (9)” for a same power output, whereas TRAD moved from “(12)” to “(10)” out of 20. Only a few studies measured the effects of training among PwMS on RPE, showing a reduction after training interventions (56). Our results suggest that individualization of training, whether by the management of the training type or the intensity, could improve the reduction of the perceived exertion, which can be considered as one key aspect of the MS-related fatigue. Although speculative, the benefits of the greater improvement in P_{\max} and $\dot{V}O_{2\text{peak}}$ for IND likely result in a lower relative percentage of maximal aerobic power being used for submaximal exercise. Consequently, for the same absolute submaximal load, the stress demands of exercise could be diminished, leading to a reduction in the RPE. This lower RPE may lead to a better perception of the constraints of “submaximal” activities of daily living (e.g., crossing the street, shopping, etc.), making them more accessible and feasible to this population. This could lead to a more active lifestyle that improves physical fitness. It would be interesting to explore more precisely the mechanisms, that is, the prevalence of afferences or corollary discharges, which explain the reduction in RPE.

Objectives Parameters

Cardiorespiratory. In line with the literature (16), we showed that exercise interventions are effective to develop different parameters of aerobic and strength capacities in PwMS. Cardiorespiratory-based interventions have been prioritized in the past because of the low aerobic capacity of these patients (57). We reported a better improvement for $\dot{V}O_{2\text{peak}}$ ($+21.0\% \pm 13.9\%$ vs $+6.8\% \pm 11.5\%$) and P_{\max} ($19.4\% \pm 11.8\%$ vs $3.4\% \pm 6.6\%$) in the IND compared with TRAD training group. Regardless of the type of intervention, the changes observed in the present study are in line with previous results showing that increases in $\dot{V}O_{2\text{max}}$ can range from

3% to 22%, and increases in P_{\max} can range from 10% to 48% after a training intervention in PwMS (58). This wide range of results between studies could be explained by the differences in the number of training sessions performed per week and the intensity (51). Although the number of sessions was the same between IND and TRAD, differences existed between the interventions. Because of the individualization design used in this study, HIIT was performed by 92% of PwMS (11/12) in the IND group, whereas only moderate continuous training was carried out in the TRAD group (see Supplemental Table 5, Supplemental Digital Content, <http://links.lww.com/MSS/D37>). More precisely, 33% of the PwMS performed only one session of HIIT, and 66% completed two sessions per week in IND (see Supplemental Table 2, Supplemental Digital Content, <http://links.lww.com/MSS/D37>). The benefits of HIIT in cardiorespiratory fitness are largely described in the literature, promoting better maximal $\dot{V}O_{2\text{peak}}$ and P_{\max} as compared with continuous training (58). Interestingly, our findings suggest that the IND training was well tolerated despite a greater intensity during HIIT and/or strength session, corroborated by higher general perceived effort. Diversifying the training by individualizing the intensity based on fatigue questionnaires and the variety of exercise training may be beneficial for improving the adherence of PwMS to a long-term exercise intervention (59,60).

In addition to performing HIIT, PwMS from the IND group underwent resistance and/or other types of endurance training. Combined training (endurance and resistance) training has been used in PwMS to understand the mixed effects of aerobic and strength training (61). The use of combined training can, however, reduce the gains in cardiorespiratory fitness compared with endurance training alone (62). To counteract this attenuation of the aerobic training effect, recent studies attempted to combine HIIT with endurance or strength training (51). Zaenker et al. (51) conducted a 12-wk program with 2/3 sessions per week with one HIIT session, one resistance session, plus an autonomous session. The authors observed a 13% and 9% increase in $\dot{V}O_{2\text{max}}$ and in maximal tolerated power, that is, greater improvements when using a combined training compared with previous studies (61,62). In a similar way, Wens et al. (63) assigned participants to one of two interventions: strength training combined either with interval (HIITR) or continuous (HICTR) training. Better results were observed on $\dot{V}O_{2\text{max}}$ improvement for the HIITR training with an increase of 17.8%, whereas HICTR induced a rise of 7.5%. In addition to showing that the combination of HIIT and resistance training is compatible to obtaining high enhancements in the cardiorespiratory level with PwMS, it provides evidence that HIIT is more effective to develop $\dot{V}O_{2\text{max}}$ than continuous training. One novelty of our study is that the IND group reached high improvement in $\dot{V}O_{2\text{peak}}$ and P_{\max} , which was usually observed with interval or endurance training only (64).

Strength. Resistance training has been largely used with PwMS leading to numerous benefits on strength, activation, or walking capacity (65). In the present study, a similar improvement of MVC between the two intervention groups was

observed. An increase of strength is usually revealed in PwMS after resistance or combined training (61,66) although less after combined training. To our knowledge, only one study explored the effects of HIIT and resistance training on neuromuscular function in PwMS. Our findings are consistent with the 10%–20% increase of isometric torque at 90° of knee extension found in this study (64). Although the number of repetitions was lower for IND compared with TRAD during strength sessions, the inclusion of HIIT in IND could stimulate the improvement of maximal strength similarly than resistance training alone (67). However, based on our individualization design, only half of the PwMS from the IND have performed strength training, leading to a disparate change in MVC after the intervention (–3% to +35%). This wide range of improvements could be due to the single IND group being formed, regardless of the origin of the weaknesses, combining patients with different training types. Future studies need to differentiate IND groups according to the deficits of each patient in order to detect the effectiveness of these individualized strategies. Individualization of intensity and exercises selected for each PwMS in IND allowed to improve the knee extensors strength and at the same time to achieve better cardiorespiratory fitness.

Fatigability. The fatigability measured by the loss of MVC torque during a submaximal cycling exercise was not improved by the training interventions for any group. In line with our results, no improvement in fatigability was found after a combined training in PwMS (68). Nevertheless, the fatigability task was reduced to two cycling stages in the present study, given that an incremental cycling test was performed in the same session. Thus, we were only able to measure fatigability after two submaximal conditions.

Although the actigraphy parameters did not differ after the two training interventions, PSQI and GLTEQ scores improved similarly. Previous investigations on the effect of exercise for PwMS reported an improvement in objective and subjective parameters of sleep (41) and physical activity (64). These discrepant results between objective and subjective parameters could be due to the adherence and accuracy of the patients to complete the sleep diary or to wear the actigraph. In addition, the parameters of physical activity and sleep were measured following testing sessions, including exercise to exhaustion, which could influence the assessment of these two variables.

CONCLUSIONS

Tailored exercise was not more effective than traditional exercise intervention to improve fatigue and other subjective parameters such as depression and quality of life in fatigued PwMS. However, compared with traditional training, individualized training resulted in greater improvements in capacities that may have positive functional consequences, particularly peak oxygen uptake, maximal aerobic power, and perceived exertion during exercise. Despite the lack of results on the main outcome of the present study (fatigue), individualization is still interesting to optimize the trainings effects in PwMS. Future studies using tailored training interventions are needed to confirm its effectiveness in promoting physical ability improvement in PwMS.

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