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Effects of long-term resistance training and simultaneous electro-stimulation on muscle strength and functional mobility in Multiple Sclerosis.

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ABSTRACT

Background. Resistance training studies in MS often use short intervention periods.

Objective. This study examined the effect(s) of unilateral long-term (20w) standardized resistance training either or not in combination with simultaneous electro-stimulation on leg muscle strength and overall functional mobility.

Methods. A randomized controlled trial was performed in 36 persons with MS. At baseline and after 10 and 20 weeks of standardized (ACSM) light to moderately intense unilateral leg resistance training (RES_o, n=11) only or resistance training with simultaneous electro-stimulation (RES_E, n=11, 100Hz, biphasic symmetrical wave, 400μs), maximal isometric strength of the knee-extensors and flexors (45°, 90° knee angle) and dynamic (60-180°/s) knee-extensor strength was measured and compared to a control group (CON, n=14). One repetition maxima were assessed and functional mobility was evaluated with the 2 Minutes Walk, Timed 25 Foot Walk, Timed Get Up and Go and Functional Reach test and the Rivermead Mobility Index.

Results. Maximal isometric knee-extensor (90°; MID: +29%; POST: +36%) in RES_o and knee-flexor (45°, POST: +40%; 90°, POST: +40%) in RES_E strength increased ($p< 0.05$) compared to CON but RES_o and RES_E did not differ between groups. Strength gains were independent of leg impairment. Also, functional reaching increased (+18%) significantly in RES_o compared to CON. Dynamic muscle strength and the remaining functional mobility tests did not change.

Conclusion. Long-term light to moderately intense resistance training improves muscle strength in persons with MS, this is independent of the level of leg impairment and simultaneous electro-stimulation does not further improve training outcome.

INTRODUCTION

Multiple sclerosis (MS) is the most common neurological disease among young to middle aged adults affecting approximately 1000000 individuals in Europe and the North Americas [1]. Although MS is characterized by many symptoms such as sensation, balance, bladder, bowel, cognitive, visual and affective deficits, it often also affects motor pathways leading to muscle weakness & muscle fatigue [2] and thus impaired functional muscle capacity and mobility [3].

Until the previous century MS patients were advised to avoid intense physical activity, because in some patients' symptoms such as fatigue were reported to worsen possibly due to an exercise induced elevation of body temperature (Uhthoff 1989). As a result, in many MS patients inactivity induced muscle atrophy and loss of muscle strength are critical factors determining daily life physical functioning as indicated by Motl and co-workers. In 2008 these investigators, indeed, showed that worsening of MS symptoms over a 3-5-year period was associated with significantly and moderately lower levels of self-reported physical activity and mobility independently of depression, neurological disability and MS-disease course [4]. In keeping with the fact that maintaining an active lifestyle is an efficient tool to reduce inactivity induced deficits in healthy persons, the impact of aerobic exercise therapy and resistance training on a broad range of functional parameters such as muscle contractile properties, quality of life and functional mobility in MS has been explored during the last decade [5,6]. To date, a growing body of evidence already suggests that regular aerobic exercise of moderate intensity does not induce MS exacerbations and improves several aspects of functional capacity [7]. Resistance training also seems to improve muscular performance [8], quality of life [5,9] and some functional mobility measures such as walking speed and walking distance [10,11]. However, effects are small, conflicting, the number of intervention studies are rather limited, the applied intervention periods are relatively short (2-8 weeks) and a wide variety of exercise interventions ranging from anti-gravity gymnastics to specific resistance training is used [5]. Therefore, it is difficult to compare between studies and to draw solid evidence based conclusions regarding the effect of resistance training in persons with MS [5]. To partly overcome this problem, exercise therapy studies in other patient populations often use standardized exercise protocols such as provided by the American College of Sports Medicine (ACSM) guidelines for resistance and/or cardiovascular exercise therapy. These protocols apply relative workloads, i.e. training at a percentage of maximal leg strength to standardize training stimuli between groups, and longer intervention periods [12]. As such, comparison between studies and pathologies is possible and long term effects can be studied in a standardized manner.

In MS central impairments such as neuronal activation failure [2] and delayed transmission velocity [13] may, in part, explain the limited effects of resistance training. Given the fact that there is a common believe that the effectiveness of resistance training can be enhanced by the addition of electrical stimulation [14], simultaneous electro-stimulation may be an interesting strategy to improve rehabilitation outcome. So far, only one study explored the use of electro-stimulation combined with active anti-gravity assisted exercise in MS [14]. Although the authors reported a treatment effect (+26% increase from initial muscle strength), a control group lacked. Consequently, this study did not provide conclusive evidence about the effectiveness of simultaneous electro-stimulation in MS.

As observed by Chung et al. many MS patients develop asymmetric leg strength during their disease course. Very often this is associated with reduced postural control and thus impaired functional mobility [15]. Therefore, the rehabilitation of unilateral muscle strength deficits may be an interesting approach to partly restore functional mobility in MS affected persons. In healthy subjects resistance training induces greater neuromuscular adaptations in weaker versus stronger muscles [16]. In the light of the underlying disease mechanisms of MS, however, it is unclear whether this relationship remains valid following resistance training in MS. In fact, to the authors' knowledge unilateral resistance training applying relative workloads to investigate strength gains in weaker versus stronger legs has not been used yet.

The present study therefore investigates the impact of a 20-week unilateral ACSM-based standardized resistance training program either or not in combination with simultaneous electro-stimulation on muscle strength and overall functional mobility in MS.

METHODS

Subjects

After being informed of all the experimental procedures to be undertaken, 36 Multiple Sclerosis (MS) patients (age 47.8 ± 10.6 yrs) complied with the inclusion criteria: (a) a definite diagnosis of MS according to McDonald criteria [17], (b) an EDSS score ranging from 2 to 6.5, and (c) a stable disease progression 12 months prior to the start of the present study. Exclusion criteria on admission were: (a) glucocorticoid treatments one month before the study start, (b) pregnancy, (c) sever psychiatric disorders, and (d) any contra-indication for light to moderate physical exercise. Furthermore, subjects were asked to maintain their normal living habits except for the physical exercise training program prescribed by the study protocol. All subjects signed a written informed consent and this study was approved by the Hasselt University Ethics Committee in accordance with the Helsinki declaration.

Study design

A randomized controlled trial was performed over a 20-week period. Baseline measurements (PRE) were randomly performed on 3 separate days interspersed by at least 48-hours recovery/rest intervals. The performed measurements involved unilateral leg muscle strength testing, evaluation of overall functional mobility and routine neurological consultations. Following baseline measurements, subjects were randomized into 3 groups matched for EDSS, age and gender by an independent investigator (Table 1). Hence, 14 subjects were assigned to the control group (CON) and maintained their normal living habits. The remaining subjects were divided in two resistance training groups undergoing ACSM-based resistance training either (RES_E, n=11) or not (RES_o, n=11) in combination with simultaneous electro-stimulation. After the first (MID) and second (POST) training period that consisted of each 10 weeks and at least 72 hours after the last training session baseline measurements were repeated by the same investigator on the same time of the day. The two training periods were separated by a two-week measurement period. Results were disclosed to the subjects and investigators until study termination.

INSERT TABLE 1 HERE

Resistance training program and simultaneous electro-stimulation

The resistance training protocol consisted of two 10-week training periods and was based on the ACSM guidelines for healthy older adults [12] applying relative workloads to improve muscular fitness. Throughout the study, subjects were instructed to participate in 5 training sessions (~60min) per fortnight. Each training session started with a standardized warm up on a cycle ergometer (5min, 30watt, 50-70 rpm). Hereafter, RES_o and RES_E subjects performed 3 leg exercises (leg press, leg extension, leg curl) on Technogym® resistance training equipment consisting of 1-2 sets of repetitions ranging from 50% of 1RM to 10 RM that were interspersed by 2-min rest intervals. After the first two training weeks, aiming to familiarize the participating subjects with resistance training procedures, the initial training load was determined by a physiotherapist and hereafter training volume and intensity were gradually increased. As shown in Table 2, training intensity was very light during the first training period. During the second training period a moderate intensity was used. Furthermore, from training session to training session subjects were instructed to increase the resistance systematically in the following session if they were able to perform the current workload for two or more repetitions over the prescribed number [18]. To monitor training workload, subjects were instructed to note the resistance used (kg) in their training diary for the 2 series of each exercise. Each training session was ended by a cooling down involving muscle stretching. Throughout the training program, subjects were encouraged and supervised by the same experienced fitness instructors (1/3 therapist - patient ratio).

Following each 10-week training period subjects were allowed to compensate for maximum 3 missed training sessions if necessary.

RES_E patients performed the same training program in combination with simultaneous electro-stimulation applied on the m. quadriceps during the leg extension and leg press. Self adhesive (Dura-stick II Chattanooga Group Inc®; Hixson, USA) electrodes 7x12.7cm were placed on the m. vastus medialis and the proximal m. vastus lateralis. During the first two training weeks subjects were familiarized with simultaneous electro-stimulation by the application of sensorial stimulation (EN-stim 4 Enraf Nonius®; Delft, The Netherlands, constant current at 100Hz, biphasic symmetrical wave, 200µs, 0,5s ramp, 3s hold, 4s rest). Hereafter, motor electro-stimulation (EN-stim 4 Enraf Nonius®; Delft, The Netherlands, constant current at 100Hz, biphasic symmetrical wave, 400µs, 3s hold, 4s rest) was applied throughout the study. To compensate for day to day variances motor stimulation intensities of each training session were set at the threshold at which a subjects' free moving lower leg reached a knee angle of 45°.

INSERT TABLE 2 HERE

Muscle strength tests

One repetition maximum (1RM). 1 RM is defined as the heaviest weight that can be lifted only once using good form [12]. This test was performed to evaluate training progression after 3, 10 and 20 weeks of training in RES_o and RES_E on the leg press, leg extension and leg curl. Briefly, first the subjects performed a light warming up of five to ten repetitions at 40 to 60% of their perceived maximum. Following a one minute rest period, three to five repetitions at 60 to 80% of the perceived maximum were executed. Then, a small amount of weight was added and a lift was attempted. If the lift was successful a recovery period of three to five minutes was provided. The goal was to find 1RM within three to five maximal efforts [12].

Dynamometry. Maximal voluntary unilateral knee-extensor and knee-flexor strength was evaluated on an isokinetic dynamometer (Biodex Medical Systems®, system 3, Inc, Shirley, New York). After a 5-min standardized warm-up on a quadriceps bench, left and right side unilateral strength tests were performed in a semi-supine (5°) sitting position. The rotational axis of the dynamometer was aligned with the transverse knee-joint axis and connected to the distal end of tibia by means of a length adjustable rigid lever arm. The upper legs, hips and shoulders were stabilized with safety belts. To evaluate maximal isometric muscle strength, subjects performed two maximal isometric knee-extensions and flexions (3s) at knee angles of 45° and 90° following one sub maximal trial contraction. Maximal contractions were interspersed by 90-s rest intervals. The highest isometric extension and flexion torques (Nm) of the manually smoothed curves at each knee angle were selected as maximal isometric torque. To measure maximal isokinetic muscle strength subjects performed four maximal consecutive isokinetic knee-extensions at a velocity of 60°/s after three sub maximal trial contractions. The knee-extensions were initiated at a joint angle of 90° to an angle of 160°. Following each extension the leg was returned passively to the starting position from which the next contraction was immediately initiated. Hereafter, the highest of four isokinetic extension torques (Nm) was selected as maximal isokinetic (60°/s) torque. Finally, and again following three sub maximal trial contractions, subjects performed twenty maximal isokinetic knee-extensions at a velocity of 180°/s to assess muscle strength endurance. The knee-extensions were initiated at a joint angle of 90° to an angle of 160°. Following each extension the leg was returned passively to the starting position from which the next contraction was immediately initiated. To determine muscle strength endurance, the average work (J) of the first three and last three contractions were compared and work fatigue, expressed as a percentage decrease, was calculated.

Spasticity

The Modified Ashworth Scale (MAS) [19] was used to measure muscle tone of left and right quadriceps, hamstrings and gastrocnemius muscles. The scale involves a five point's ordinal scale.

EDSS & functional mobility

A qualified research neurologist examined the participating subjects. Briefly, this included their medical history, a routine neurological examination and the determination of each individuals' disease severity using the Expanded Disability Status Scale (EDSS) [20]. Furthermore, overall functional mobility was assessed using a variety of different functional mobility tests such as the Timed Up and Go (TUG) [21], the Timed 25 Foot Walk (T25FW) [22], the Two Minutes Walk Test (2MWT) [23], the Functional Reach (FR) [24] and the Rivermead Mobility Index (RMI) [25] self reported scale.

Statistical analyses

Statistical analyses were performed using SAS® software (Version 9.2; SAS Institute, Inc., Cary, NC). Baseline differences between groups were analyzed using one-way ANOVA's. Training effects on muscle strength (individual averages of right and left legs) and functional mobility were analyzed by means of a 3x3 ([CON, RES_o, RES_E] x [PRE, MID, POST]) repeated measures ANOVA (GLM) using the least square method. One repetition maxima (individual averages of right and left legs) data were analyzed using 2x3 ([RES_o, RES_E] x [week3, week10, week20]) repeated measures ANOVA (GLM). When appropriate, pre-planned post hoc contrast analyses were used to determine time and/or group x time effects. If data distribution was abnormal, they were normalized and compared with the statistical outcome of the original data set. If no differences in outcome were found, the original data set was used.

To explore the impact of resistance training on mildly, moderately and severely impaired muscle strength, single leg isometric and isokinetic peak torque data were used. To distinguish between impairment levels, pooled RES_o and RES_E legs, and CON legs were divided into mildly (≥+1 SD; RES_{mi}, CON_{mi}), moderately (±1SD; RES_{mo}, CON_{mo}) and severely (≤-1SD; RES_s, CON_s) affected muscle strength groups. These three different leg impairment levels were calculated based on the mean of each isometric and isokinetic baseline value of all subjects. Hereafter, a 2x3X3 (group [RES, CON] x 3 [PRE, MID, POST] x 3 impairment level [mild, moderate, severe]) ANOVA for repeated measurements and pre-planned post hoc contrast analysis were used to determine time, group and impairment level effects when appropriate. Muscle tone of the different muscles (individual averages of right and left muscle) was analyzed using the non-parametric Friedman test. The level of statistical significance was set at $p<0.05$ and data are presented as mean ± SE.

RESULTS

Drop out and compliance

During the study, two CON and one RES_E patients retreated due to either a severe relapse, perceived lack of time to continue the study and a mild stroke unrelated to this study, respectively. In total, 1050 resistance training sessions were planned. Twelve of which were not executed resulting in a ~99% compliance.

Baseline measurements.

Baseline muscle strength, spasticity and functional mobility values did not differ ($p>0.05$) between groups, except for leg press 1RM between RES_o and RES_E ($p<0.05$).

Muscle strength.

One repetition maximum (1RM). To evaluate leg press, leg extension and leg curl training progression, ACSM-based one repetition maxima tests were performed in RES_o and RES_E following 3, 10 and 20 weeks of training. Throughout the study period no differences between RES_o and RES_E (group x time) were found. However, as indicated in Table 3, training load increased gradually in both intervention groups. During the first 10 training weeks, in RES_o and RES_E weights increased with ~17% and ~19% (leg press), ~12% and ~10% (leg extension) and ~7% and ~17% (leg curl), respectively. Compared to baseline, 20 weeks of training further increased training loads by ~47% and ~36% (leg press), ~31% and ~30% (leg extension) and ~31% and ~44% (leg curl) in RES_o and RES_E.

INSERT TABLE 3 HERE

Maximal isometric muscle strength. As shown in Table 4, significant interaction effects (group x time) were found. Whereas CON knee-extensor and knee-flexor maximal isometric peak torque remained stable or decreased ($p<0.05$) throughout the study period, isometric muscle strength increased in RES_o and RES_E. At a knee angle of 90° post hoc contrast analysis in RES_o indicated a higher isometric knee extension torque compared to CON following 10 (+29%) and 20 (+36%) weeks of resistance training. At knee angles of 45° and 90° knee flexion torques following 20 weeks of RES_E were ~40% higher compared to CON. Within group effects are indicated in the Table.

Maximal isokinetic muscle strength. No significant interaction effects (group x time) were found (Table 3). However, whereas in CON knee-extensor isokinetic peak torque remained stable throughout the study period, contrast analysis following a time effect indicated significant strength gains in RES_o (+15%) and RES_E (+12%) after 20 weeks.

Muscle strength endurance. As shown in Table 4 no significant interaction effects (group x time) were found. Compared to the corresponding baseline values work fatigue, expressed as a percentage decrease, following 10 and 20 weeks of training significantly decreased in RES_o (MID: -16%, POST: -13%) and RES_E (MID: -7%, POST: -15%) but also in CON (MID: -4%, POST: -13%).

INSERT TABLE 4 HERE

Leg impairment level strength analysis. Because maximal muscle strength measurements and resistance training of all subjects were performed on each leg separately, single leg strength analyses were performed on pooled RES_o and RES_E data. Pooled RES and CON legs were then divided in three different levels, notably mildly- ($_{mi}$), moderately- ($_{mo}$) and severely ($_{s}$) impaired legs (see Methods for further details). Hence, these three leg impairment levels have gradually and significantly higher baseline strength values that did not differ between RES and CON. (Table 4). Furthermore, no significant group x time x impairment level effect was found indicating a similar training response between mildly, moderately and severely impaired legs. However, when taken as a whole, in RES maximal isometric knee-extensor (45°, $p = 0.03$ and 90°, $p = 0.01$) and knee flexor (45°, $p < 0.01$ and 90°, $p = 0.03$) strength improved significantly (group x time) compared to the CON group.

INSERT TABLE 5 HERE

Spasticity

MAS. As shown in Table 6, spasticity group x time analysis indicated an overall interaction effect (right legs $p=0.01$; left legs $p=0.06$ [statistical trend]). Furthermore, compared to baseline the muscle tone of the right quadriceps in RES_E and the left quadriceps in RES_o decreased substantially. In the hamstrings and gastrocnemius no changes were detected.

INSERT TABLE 6 HERE

EDSS & functional mobility

Throughout the study period EDSS remained stable. Exercise therapy affected reaching distance (group x time) significantly. Here, in RES_o post hoc contrast analysis showed increased (+18%) reaching distance compared to CON following 10 weeks of training. The 2MWT, T25FW, TUG and RMI were unaffected in all groups (Table 7).

INSERT TABLE 7 HERE

DISCUSSION

Reduced muscle capacity and functional mobility are important debilitating symptoms affecting quality of life in MS [26]. Recently it has been observed that short [11,27,28] and longer-term [29] high-intensity resistance training programs can improve muscle strength. Here we demonstrate that a standardized 20-week light to moderately intense unilateral resistance training program improves isometric leg muscle strength with 8 to 10%, independent of the initial level of leg impairment. Simultaneous electro-stimulation had no additional effects and functional mobility did not improve in this patient sample.

Muscle functional capacity is an important component of health related fitness [18,30,31]. Consequently, diminished muscular performance reduces mobility and thus impairs quality of life. Recent observations, following moderate to high intensity short-term [10,11,28] and longer-term [29] rehabilitation programs in MS, indicated improved muscular performance. Based on the existing literature, however, the optimal training duration (are effects more pronounced after long-term training?) and intensity (is low intensity training also effective?) remains unclear. The low to moderately intense resistance training regimen, applied in the present study, improved maximal isometric (45°: RES_o +8.3%, RES_E +6.2%; 90°: RES_o +9.9%) and isokinetic (60°/s: RES_o +11.5%) knee extension torque after 10 weeks whereas no changes were observed in the control group. Consistent with our findings, White et al. [11] demonstrated comparable knee-extensor strength gains (+7.2%) after an 8-week though comparable ACSM based resistance training protocol. These findings were paralleled by the obtained 1RM data during the training period. Here, compared to baseline, 1RM values at 10 weeks increased ($p<0.05$; within group effect) during leg press (RES_o: 16%, RES_E: 18%), leg extension (RES_o: 12%, RES_e: 10%) and leg curl (RES_o: 7%, RES_E: 17%) exercises. During the second study phase, exercise intensity/volume was augmented. Hence, further strength increases were assumed [12] to be present. However, whereas in

CON maximal isometric knee-extensor (90°: -6.9%) and flexor (45°: -10.6%; 90°: -9.4%) muscle strength decreased during the second study period, muscle strength did not further improve in the experimental groups (Table 4). To the authors' knowledge, this is the first training study in MS that applies an intermediary measurement session. Therefore, it is unclear whether this observation suggests a maximal training effect in persons with MS as reported in healthy individuals or an MS-specific mechanism that prevents further improvements.

Notwithstanding the fact that in the present study and in the work of White et al. [11] muscle strength increased significantly, it must be noted that effects are rather small. Indeed, normal training progressions usually obtained in healthy older or mid-age populations, using similar resistance training programs, range from 15 to 30% [32,33] or from 10-25% in neuromuscular disorders such as spinal muscular dystrophy [34] and post polio [35]. Applying a 12-week moderate to high intensity training protocol Dalgas et al. demonstrated a ~16% increase in maximal voluntary knee-extensor strength in persons with MS [29]. The current study, however, aimed to maximize training adherence and tolerance by virtue of low to moderately intense exercises. This resulted in a training session compliance of ~99% and a drop-out of only 3 patients out of 36. Similar to White et al. [11], however, the low to moderately intense training regimen of the present study might have been an insufficient training stimulus to evoke larger strength gains caused. On the one hand, this may be caused by the fact that the magnitude of muscle fiber atrophy in MS subjects is approximately double that observed in the knee-extensors of healthy subjects [36]. Hence, a longer rehabilitation period is required. On the other hand, chronically reduced maximal discharge rates [37] and altered or incomplete motor unit activation [38] may have reduced exercise stimulus efficiency.

In an attempt to improve resistance training efficiency in MS, we applied simultaneous peripheral electro-stimulation in a separate resistance training group (RES_E) during knee-extensor exercises. Unfortunately, this application did not further enhance strength gains. Our results match with reviewed findings by Paillard and co-workers [39] who reported that the integration of superimposed electrical stimulation in a healthy population did not bring further benefits compared with training programs using only volitional exercises. Despite the fact that simultaneous electro-stimulation did not further improve training efficiency, it must be noted that the participants of the present study repeatedly declared that the applied electro-stimulation guided them through their strength exercise because contraction speed and duration as well as the number of executions were indicated. In keeping with the fact that many persons with MS have cognitive problems, simultaneous electro-stimulation might help them to perform resistance training exercises.

An unilateral strength training regimen was applied because many MS patients show asymmetric leg strength deficits [15]. Doing so, we hypothesized that optimal training stimuli could be provided to the affected leg muscles by virtue of unilateral relative training loads. The present data indicate similar training responses in weaker versus stronger legs (Table 6). This new finding is important for neurorehabilitation as it indicates that weak muscles also have training potential for strength improvement. In fact, it may suggest that muscular adaptations following resistance training in MS are, at least in part, independent of the severity of muscle weakness. This is probably disuse associated but other tentative mechanisms such as greater cortical mapping following exercise therapy might be worthwhile to investigate.

Functional mobility is another important component of health related fitness that is strongly correlated with muscle functional capacity [18,31]. In fact, muscle strength has been defined as a important predictor of ambulatory function [40]. Given the above described increases in muscle strength, improved functional mobility and gait kinematics could be assumed as indicated by Seguin in normal healthy subjects [33] and Gutierrez and Gijbels in persons with MS [10] (Gijbels, manuscript under revision in Multiple Sclerosis). However, with the exception of functional reach, none of the applied functional mobility measures improved in our MS patient samples. This could be explained by the fact that throughout the study course, participants did not specifically train functional mobility. Our results mirror data from White and co-workers [11] who were unable to detect improved walking speed following

8 weeks of regular resistance training in persons with MS. This probably suggests the need for specific training to improve functional mobility. Interestingly, in the present study, functional reach improved. Of course, this may be caused by enhanced lower back or hamstring flexibility following stretching during the cooling down of each training session but given the fact that functional reaching involves active hip and knee muscle control this might be a genuine effect of the applied exercise regimen. In the light of the former precautionary stance towards exercise and MS it is important to note that the applied strength training regimen did not induce spasticity (Table 6) and over the 20 weeks, no deterioration of the EDSS score was found in any of the experimental groups.

In conclusion, the current study shows that long-term individualized low to moderately intense resistance training improves muscle strength independent of the level of leg impairment. Simultaneous electro-stimulation did not have an additional effect and the applied training regimen did not improve functional mobility.

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REFERENCE

1. **Kantarci OH, Barcellos LF, Atkinson EJ, Ramsay PP, Lincoln R, Achenbach SJ** *et al.* Men transmit MS more often to their children vs women: the Carter effect. *Neurology* 2006; **67(2)**: 305-10.

2. **de HA, de Ruiter CJ, van Der Woude LH, Jongen PJ.** Contractile properties and fatigue of quadriceps muscles in multiple sclerosis. *Muscle Nerve* 2000; **23(10)**: 1534-41.

3. **White LJ, Dressendorfer RH.** Exercise and multiple sclerosis. *Sports Medicine* 2004; **34(15)**: 1077-100.

4. **Motl RW, Arnett PA, Smith MM, Barwick FH, Ahlstrom B, Stover EJ.** Worsening of symptoms is associated with lower physical activity levels in individuals with multiple sclerosis. *Mult Scler* 2008; **14(1)**: 140-2.

5. **Dalgas U, Stenager E, Ingemann-Hansen T.** Multiple sclerosis and physical exercise: recommendations for the application of resistance-, endurance- and combined training. *Mult Scler* 2008; **14(1)**: 35-53.

6. **Motl RW, Gosney JL.** Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis. *Mult Scler* 2008; **14(1):** 129-35.

7. **Smith RM, Adeney-Steel M, Fulcher G, Longley WA.** Symptom change with exercise is a temporary phenomenon for people with multiple sclerosis. *Arch Phys Med Rehabil* 2006; **87(5)**: 723-7.

8. **Taylor NF, Dodd KJ, Prasad D, Denisenko S.** Progressive resistance exercise for people with multiple sclerosis. *Disability & Rehabilitation* 2006; **28(18)**: 1119-26.

9. **Motl RW, McAuley E, Snook EM.** Physical activity and multiple sclerosis: a meta-analysis. *Mult Scler* 2005; **11(4)**: 459-63.

10. **Gutierrez GM, Chow JW, Tillman MD, McCoy SC, Castellano V, White LJ.** Resistance Training Improves Gait Kinematics in Persons With Multiple Sclerosis. *Arch Phys Med Rehabil* 2005; **86(9)**: 1824-9.

11. **White LJ, McCoy SC, Castellano V, Gutierrez G, Stevens JE, Walter GA** *et al.* Resistance training improves strength and functional capacity in persons with multiple sclerosis. *Mult Scler* 2004; **10(6)**: 668-74.

12. **Baladay GJ, Berra KA, Golding LA, Gordon NF, Mahler DA, Myers JN** *et al.* ACSM's Guidelines for Exercise Testing and Prescrition. 2000.

13. **Nielsen JF.** Frequency-dependent conduction delay of motor-evoked potentials in multiple sclerosis. *Muscle Nerve* 1997; **20(10)**: 1264-74.

14. **Glinsky J, Harvey L, Van EP.** Efficacy of electrical stimulation to increase muscle strength in people with neurological conditions: a systematic review. *Physiother Res Int* 2007; **12(3)**: 175-94.

15. **Chung LH, Remelius JG, Van Emmerik RE, Kent-Braun JA.** Leg power asymmetry and postural control in women with multiple sclerosis. *Med Sci Sports Exerc* 2008; **40(10)**: 1717-24.

16. **Kraemer WJ, Adams K, Cafarelli E, Dudley GA, Dooly C, Feigenbaum MS** *et al.* American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2002; **34(2)**: 364-80.

17. **McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD** *et al.* Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001; **50(1)**: 121-7.

18. **Kraemer WJ, Ratamess NA, French DN.** Resistance training for health and performance. *Curr Sports Med Rep* 2002; **1(3)**: 165-71.

19. **Bohannon RW, Smith MB.** Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther* 1987; **67(2)**: 206-7.

20. **Kurtzke JF.** Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; **33(11)**: 1444-52.

21. **Podsiadlo D, Richardson S.** The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991; **39(2)**: 142-8.

22. **Nilsagard Y, Lundholm C, Gunnarsson LG, Dcnison E.** Clinical relevance using timed walk tests and 'timed up and go' testing in persons with multiple sclerosis. *Physiother Res Int* 2007; **12(2)**: 105-14.

23. **Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM.** Two-, six-, and 12-minute walking tests in respiratory disease. *Br Med J (Clin Res Ed)* 1982; **284(6329)**: 1607-8.

24. **Duncan PW, Weiner DK, Chandler J, Studenski S.** Functional reach: a new clinical measure of balance. *J Gerontol* 1990; **45(6)**: 192-197.

25. **Collen FM, Wade DT, Robb GF, Bradshaw CM.** The Rivermead Mobility Index: a further development of the Rivermead Motor Assessment. *Int Disabil Stud* 1991; **13(2)**: 50-4.

26. **Ng AV, Kent-Braun JA.** Quantitation of lower physical activity in persons with multiple sclerosis. *Med Sci Sports Exerc* 1997; **29(4)**: 517-23.

27. **Taylor N.F., Dodd K.J., Prasad D., DenisenkoS.** Progressive resistance exercise for people with multiple sclerosis. *Disability and Rehabilitation* 2005; **28**: 1119-1126.

28. **Souza-Teixeira FD, Costilla S, Ayan C, Garcia-Lopez D, Gonzalez-Gallego J, Paz JA.** Effects of Resistance Training in Multiple Sclerosis. *Int J Sports Med* February 6 2009.(**DOI** 10.1055/s-0028-1105944)

29. **Dalgas U, Stenager E, Jakobsen J, Petersen T, Hansen HJ, Knudsen C** *et al.* Resistance training improves muscle strength and functional capacity in multiple sclerosis. *Neurology* 2009; **73(18)**: 1478-84.

30. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2009; **41(3)**: 687-708.

31. **Bouchard C.** *Exercise, fitness, and health: The consensus statement.* 1990.

32. **Eijnde BO, Van LM, Goris M, Labarque V, Taes Y, Verbessem P** *et al.* Effects of creatine supplementation and exercise training on fitness in men 55-75 yr old. *J Appl Physiol* 2003; **95(2)**: 818-28.

33. **Seguin R, Nelson ME.** The benefits of strength training for older adults. *Am J Prev Med* 2003; **25(3 Suppl 2)**: 141-9.

34. **McCartney N, Moroz D, Garner SH, McComas AJ.** The effects of strength training in patients with selected neuromuscular disorders. *Med Sci Sports Exerc* 1988; **20(4)**: 362-8.

35. **Spector SA, Gordon PL, Feuerstein IM, Sivakumar K, Hurley BF, Dalakas MC.** Strength gains without muscle injury after strength training in patients with postpolio muscular atrophy. *Muscle Nerve* 1996; **19(10)**: 1282-90.

36. **Kent-Braun JA, Le BR.** Quantitation of central activation failure during maximal voluntary contractions in humans. *Muscle Nerve* 1996; **19(7)**: 861-9.

37. **Rice CL, Vollmer TL, Bigland-Ritchie B.** Neuromuscular responses of patients with multiple sclerosis. Muscle Nerve 1992; **15(10)**: 1123-32.

38. **Kent-Braun JA, Sharma KR, Weiner MW, Miller RG.** Effects of exercise on muscle activation and metabolism in multiple sclerosis. *Muscle Nerve* 1994; **17(10)**: 1162-9.

39. **Paillard T, Noe F, Passelergue P, Dupui P.** Electrical stimulation superimposed onto voluntary muscular contraction. *Sports Med* 2005; **35(11)**: 951-66.

40. **Kim CM, Eng JJ, Whittaker MW.** Level walking and ambulatory capacity in persons with incomplete spinal cord injury: relationship with muscle strength. *Spinal Cord* 2004; **42(3)**: 156-62.

Tables

Table 1. Subject characteristics

	RES_o	RES_E	CON	p
n	11	11	14	0.18
♀/♂	6 / 5	6 / 5	11 / 3	0.20
EDSS (arbitrary units)	4.5 ± 1.3	4.4 ± 0.9	4.1 ± 1.1	0.72
Age (years)	44.9 ± 11.6	48.7 ± 8.6	49.7 ± 11.3	0.53
PASAT (arbitrary units)	41.3 ± 4.8	45.0 ± 3.9	38.8 ± 2.6	0.35

Values are numbers or means ± SE and represent baseline subject characteristics (EDSS: Expanded Disability Status Scale; PASAT: Paced Auditory Serial Addition Task) of the control (CON) group and the resistance training groups either (RES_E) or not (RES_o) in combination with simultaneous electro-stimulation. P values represent baseline differences. See Methods for further details.

Table 2. Volume and intensity of the resistance training program

Weeks	Goal	Volume	Intensity
-3-0	Baseline testing		
1-2	Familiarization	1x10	Minimal resistance
3-6	increase in intensity	1x10	50-60% 1RM
7-8	increase in volume	2x10	60% 1RM
9-10	increase in volume	2x12	60% 1RM
2 weeks	MID testing		
11		2x12	60%1RM
12-14	increase in volume	2x15	15RM
15-17	increase in intensity	2x12	12RM
18-20	increase in intensity	2x10	10RM
2 weeks	POST testing		

Table 3. One repetition maxima (1RM in Kg).

	week	RES_o (n=9)	RES_E (n=9)
Leg Press	3	30.6 ± 4.3	48.2 ± 9.0
	10	35.7 ± 6.0	57.2 ± 7.2
	20	44.8 ± 5.5 †,‡	65.6 ± 7.4 †,‡
Leg Extension	3	19.3 ± 2.7	21.4 ± 2.8
	10	21.6 ± 3.2 †	23.6 ± 2.4 †
	20	25.2 ± 3.1 †,‡	27.9 ± 2.6 †,‡
Leg Curl	3	16.9 ± 2.0	17.9 ± 2.2
	10	18.1 ± 2.5	21.0 ± 2.8 †
	20	22.2 ± 2.0 †,‡	25.7 ± 2.7 †,‡

Values are means ± SE and represent 1RM of the resistance training groups either (RES_E) or not (RES_o) in combination with simultaneous electro-stimulation after 3, 10 and 20 weeks of training. P values represent † $P < 0.05$ compared to the corresponding baseline value and ‡ $P < 0.05$ compared to the corresponding MID value. See Methods for further details.

Table 4. Muscle contractile data.

ISOMETRIC (Nm)			p	RES_o (n=11)	RES_E (n=10)	CON (n=12)
Extensor	45	PRE	0.19	128.1 ± 12,4	116.8 ± 10.6	97.7 ± 9.5
		MID		138.8 ± 13.5 †	124.1 ± 8.5 †	97.0 ± 9.2
		POST		138.9 ± 12.8 †	123.5 ± 9.0	93.0 ± 9.1
	90	PRE	0.01	107.5 ± 9.1	103.8 ± 9.9	93.3 ± 9.8
		MID		118.1 ± 11.0 †,*	107.2 ± 9.3	90.8 ± 11.0
		POST		117.5 ± 10.4 †,*	106.3 ± 8.7	86.9 ± 9.6 †
Flexor	45	PRE	0.03	56.3 ± 6.2	59.0 ± 6.6	49.9 ± 5.0
		MID		60.0 ± 6.6	62.1 ± 7.3	46.3 ± 5.0
		POST		60.3 ± 6.3	62.7 ± 7.1 *	44.6 ± 4.5 †
	90	PRE	0.04	44.6 ± 5.2	49.2 ± 5.9	41.7 ± 3.5
		MID		46.9 ± 5.6	52.2 ± 6.4	39.1 ± 4.0
		POST		46.9 ± 5.1	53.2 ± 6.2 *	37.8 ± 3.1 †
ISOKINETIC (Nm)						
Extensor 60°/s		PRE	0.16	101.3 ± 10.6	94.1 ± 10.3	87.9 ± 11.5
		MID		110.6 ± 11.3 †	98.2 ± 9.9	87.9 ± 12.6
		POST		116.6 ± 12.4 †	105.0 ± 8.9 †	87.6 ± 11.6
ENDURANCE (Δ%)						
Work fatigue Extensor 180°/s		PRE	0.23	32.7 ± 4.1	25.3 ± 2.8	31.6 ± 4.0
		MID		27.5 ± 4.6 †	23.7 ± 3.2 †	30.5 ± 2.7 †
		POST		28.5 ± 4.2 †	21.5 ± 2.5 †	27.5 ± 3.7 †

*Values are means ± SE and represent peak knee extensor and flexor isometric (ISOM) and isokinetic (ISOK) torque (Nm) and work fatigue (ENDURANCE). Work fatigue was calculated as a percentage decrease (Δ%). Measurements were performed before (PRE) and following 10 (MID) and 20 (POST) weeks of control conditions (CON) or guided exercise training either (RES_E) or not (RES_o) in combination with simultaneous electro-stimulation. P values represent time x group interaction effects † $P < 0.05$ compared to the corresponding baseline value and * $p < 0.05$ compared to the corresponding CON value. See Methods for further details.*

Table 5. Peak knee extensor and flexor isometric and isokinetic muscle strength at different leg impairment levels.

ISOM		p		n	RES_s	n	CON_s	n	RES_{mo}	n	CON_{mo}	n	RES_{mi}	n	CON_{mi}
Extensor	45	0.50	PRE	11	76.6 ± 3.9	10	68.4 ± 6.7	12	113.1 ± 3.4	10	104.7 ± 2.1	19	155.5 ± 5.9	4	153.3 ± 9.1
			MID	11	90.0 ± 4.8	10	71.7 ± 5.6	12	121.3 ± 6.4	10	100.6 ± 2.8	19	162.2 ± 7.3	4	151.6 ± 15.0
			POST	11	88.2 ± 7.4	10	68.8 ± 4.9	12	126.3 ± 6.5	10	94.5 ± 4.4	19	160.1 ± 6.4	4	150.0 ± 12.6
	90	0.30	PRE	14	70.0 ± 2.5	11	64.2 ± 4.5	13	102.3 ± 2.8	8	99.6 ± 3.0	15	142.2 ± 4.4	5	147.4 ± 11.6
			MID	14	76.0 ± 3.4	11	63.4 ± 4.4	13	110.5 ± 3.6	8	90.4 ± 3.0	15	149.6 ± 5.6	5	151.6 ± 17.3
			POST	14	75.5 ± 3.3	11	59.2 ± 4.2	13	114.9 ± 5.7	8	92.5 ± 3.7	15	144.2 ± 5.5	5	139.1 ± 12.0
Flexor	45	0.90	PRE	12	32.0 ± 2.3	7	27.8 ± 4.6	13	51.7 ± 1.2	14	54.1 ± 1.8	17	80.3 ± 2.6	3	82.4 ± 6.8
			MID	12	37.1 ± 3.2	7	27.8 ± 3.6	13	54.2 ± 2.9	14	50.6 ± 2.5	17	83.1 ± 3.6	3	75.9 ± 12.2
			POST	12	38.1 ± 4.0	7	24.3 ± 3.1	13	57.6 ± 2.8	14	49.5 ± 2.4	17	81.0 ± 3.7	3	69.2 ± 7.5
	90	0.20	PRE	9	18.8 ± 3.2	7	27.5 ± 3.6	18	45.2 ± 1.2	13	42.9 ± 1.1	15	65.7 ± 2.8	4	62.9 ± 6.0
			MID	9	23.0 ± 3.8	7	27.0 ± 3.0	18	47.5 ± 2.5	13	38.0 ± 1.4	15	67.8 ± 3.3	4	63.8 ± 8.1
			POST	9	24.3 ± 3.7	7	23.9 ± 2.0	18	47.8 ± 2.3	13	39.9 ± 1.9	15	68.0 ± 3.6	4	54.9 ± 4.2
ISOK															
Extensor 60°/s		0.64	PRE	15	55.8 ± 3.4	7	51.9 ± 8.6	11	94.2 ± 3.2	13	93.5 ± 3.2	16	140.2 ± 4.5	4	147.7 ± 15.5
			MID	15	93.4 ± 8.8	7	67.2 ± 15.3	11	90.5 ± 9.5	13	86.0 ± 10.1	16	125.3 ± 8.7	4	130.3 ± 28.5
			POST	15	100.4 ± 9.2	7	72.9 ± 14.7	11	97.9 ± 10.8	13	86.5 ± 10.8	16	130.2 ± 9.4	4	116.7 ± 24.7

Values are means ± SE and represent peak knee extensor and flexor isometric (ISOM) and isokinetic (ISOK) torque (Nm) before (PRE) and following 10 (MID) and 20 (POST) weeks of control conditions or resistance exercise (RES) subdivided in different leg impairment levels (severely: s, moderately: mo, mildly: mi). P values represent time x group x impairment level interaction effects. See Methods for further details.

Table 6. Modified Ashworth data.

			p	RES_o (n=11)	RES_E (n=10)	CON (n=12)
Quadriceps	Right	PRE	0.06	0.3 ± 0.14	0.6 ± 0.16	0.5 ± 0.23
		MID		0.1 ± 0.09	0.1 ± 0.10	0.2 ± 0.11
		POST		0.2 ± 0.12	0.1 ± 0.10 †	0.3 ± 0.13
	Left	PRE	0.01	0.5 ± 0.28	0.6 ± 0.30	0.6 ± 0.34
		MID		0.1 ± 0.09	0.4 ± 0.22	0.3 ± 0.18
		POST		0.0 ± 0.00 †	0.2 ± 0.13	0.1 ± 0.08
Hamstrings	Right	PRE	0.31	0.2 ± 0.12	0.2 ± 0.13	0.1 ± 0.08
		MID		0.1 ± 0.09	0.0 ± 0.00	0.2 ± 0.11
		POST		0.1 ± 0.09	0.0 ± 0.00	0.1 ± 0.08
	Left	PRE	0.61	0.1 ± 0.09	0.1 ± 0.10	0.3 ± 0.33
		MID		0.0 ± 0.00	0.2 ± 0.20	0.2 ± 0.16
		POST		0.0 ± 0.00	0.1 ± 0.10	0.2 ± 0.17
Gastrocnemius	Right	PRE	0.92	1.4 ± 0.36	0.7 ± 0.21	0.7 ± 0.26
		MID		0.7 ± 0.24	0.7 ± 0.15	0.6 ± 0.19
		POST		0.6 ± 0.28	0.9 ± 0.10	0.8 ± 0.18
	Left	PRE	0.32	1.3 ± 0.45	0.6 ± 0.16	0.9 ± 0.34
		MID		0.7 ± 0.24	0.6 ± 0.16	0.8 ± 0.22
		POST		0.6 ± 0.28	0.7 ± 0.15	0.5 ± 0.19

Values are means ± SE and represent muscle tones of three different unilateral muscle groups before (PRE) and following 10 (MID) and 20 (POST) weeks of control conditions (CON) or guided exercise training either (RES_E) or not (RES_o) in combination with simultaneous electro-stimulation. P values represent time x group interaction effects † P < 0.05 compared to the corresponding baseline value. See Methods for further details.

Table 7. Functional mobility data.

		p	n	RES$_o$		n	RES$_E$		n	CON
T25FW	PRE	0.25	9	6.2 ± 0.7		9	5.4 ± 0.4		11	5.8 ± 0.4
	MID		9	5.7 ± 0.5		9	5.1 ± 0.4		11	6.0 ± 0.5
	POST		9	5.9 ± 0.6		9	5.2 ± 0.3		11	5.6 ± 0.4
FR	PRE	<0.01	11	31.7 ± 1.5		10	29.7 ± 1.9		12	30.5 ± 1.2
	MID		11	33.3 ± 2.2	*	10	32.5 ± 1.3		12	27.7 ± 1.8
	POST		11	30.2 ± 1.8	‡	10	32.7 ± 1.4	†	12	28.6 ± 1.6
TUG	PRE	0.2	10	8.2 ± 0.7		9	7.1 ± 0.5		11	7.7 ± 0.5
	MID		10	7.8 ± 0.7		9	6.8 ± 0.5		11	8.2 ± 0.7
	POST		10	7.8 ± 0.5		9	6.7 ± 0.6		11	8.1 ± 0.4
2MWT	PRE	0.42	9	166.8 ± 8.5		9	178.2 ± 12.7		11	165.7 ± 6.9
	MID		9	177.0 ± 6.7		9	182.2 ± 11.6		11	164.6 ± 7.8
	POST		9	174.3 ± 8.7		9	184. ± 11.8		11	167.5 ± 6.8

*Values are means ± SE and represent timed 25 foot walking test (T25FWT), functional reach (FR), Timed get up and go (TUG) and 2 minutes walk test (2MWT) before (PRE) and following 10 (MID) and 20 (POST) weeks of control conditions (CON) or guided exercise training either (RES$_E$) or not (RES$_o$) in combination with simultaneous electro-stimulation. P values represent time x group interaction effects † $P < 0.05$ compared to the corresponding baseline value, ‡ $P < 0.05$ compared to the corresponding MID value and * $p < 0.05$ compared to the corresponding CON value. See Methods for further details.*