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Research Paper

Neuromuscular adaptations to long-term progressive resistance training translates to improved functional capacity for people with multiple sclerosis and is maintained at follow-up

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Abstract

Background: Progressive resistance training (PRT) is acknowledged to effectively improve muscle strength for people with multiple sclerosis (PwMS), but diverging results exist regarding whether such improvements translates to improved functional capacity, possibly relating to insufficient duration and/or intensity in some previous studies.

Objective: The purpose of this study was to evaluate potential changes in functional capacity and neuromuscular function after 24 weeks of supervised PRT, and whether improvements are maintained after an additional 24 weeks of self-guided exercise.

Methods: This study was a randomised controlled trial, with a training group and a waitlist group undergoing supervised PRT for 24 weeks initially or after 24 weeks of habitual lifestyle, respectively. Functional capacity, isometric muscle strength of knee extensors and flexors, neural drive and thigh muscle cross-sectional area was measured at baseline, after 24 and 48 weeks.

Results: The training group significantly improved neuromuscular function of the knee extensors and flexors, which translated to improvements in functional capacity. Furthermore, the improved functional capacity was maintained after 24 weeks of self-guided physical activity. The waitlist group produced similar patterns of changes after PRT.

Conclusion: Compelling evidence is provided, that PRT performed over sufficiently long periods, improves functional capacity, likely due to neuromuscular adaptations.

Keywords: Multiple sclerosis, resistance training, rehabilitation, muscle strength, walking

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Introduction

Multiple sclerosis (MS) is a chronic, auto-immune and demyelinating disease of the central nervous system (CNS), characterised by heterogeneous and complex symptoms.[1] When asked, people with MS (PwMS) rate impaired mobility as the most critical symptom.[2] Impaired mobility is treated medically with 4-aminopyridine (a potassium channel blocker), but only 40% of PwMS respond positively.[3] Consequently, non-pharmacological interventions that can maintain or even improve functional capacity are highly warranted in MS rehabilitation.

Lower body muscle strength, which is impaired for PwMS,[4] is a well-established predictor of walking speed.[5] In a recent review, it was highlighted that progressive resistance training (PRT) effectively improves muscle strength.[6] However, it was further concluded that divergent results exist on whether the achieved strength translates to improved functional capacity,[7–9] which likely relate to considerable variations in training duration.[6] Moreover, it is likely that prolonged interventions applying higher training intensity will have a more consistent effect on functional capacity. Another deficient muscle mechanical parameter for

PwMS is rate of force development (RFD),[10,11] which is suggested to be important for functional capacity in frail populations by controlling balance and preventing falls.[12] Since maximal muscle strength and RFD deficits for PwMS are related to both neural (reduced neural drive and muscle activation)[11,13] and muscular (reduced muscle size and altered fibre type distribution)[14] mechanisms, and since high intensity resistance exercise is highly reliant on neural drive, the latter seem to constitute a sensible exercise strategy for PwMS. In healthy populations, improvements of both neural and muscular parameters are observed following PRT,[15,16] but adaptations in RFD and the underlying neural and muscular mechanisms have only been scarcely investigated in PwMS.[6] Investigations of neural adaptations to PRT shows improved neural drive[17,18] but unaltered central activation,[19] while investigations of muscular adaptations report hypertrophy of muscle fibres,[20] but diverging results for whole-muscle cross-sectional area (CSA).[19,21] Despite the promising findings and the importance of understanding the mechanisms underlying muscle strength adaptations in PwMS, only one previous randomised controlled trial (RCT) has reported on both neural and muscular adaptations following short term PRT,[18,20] thus warranting further research.

In regards to measures of functional capacity, previous studies of PRT for PwMS have focused exclusively on objective measures such as maximal walking speed.[6] However, self-reported measures covering broader aspects of functional capacity, such as the validated[22] and responsive[23] 12-item MS Walking Scale (MSWS-12),[24] have not been evaluated until now. Given that physical disabilities are considered one of the most critical symptoms by PwMS,[2] further investigation of PRT effects on self-reported outcomes seems relevant.

Another important topic is whether improvements in muscle strength and functional capacity obtained following supervised PRT can be maintained after subsequent self-guided physical activity. Dalgas et al.[7] reported that training-induced changes were maintained 12 weeks after completion of PRT when participants continued training in an independent non-controlled manner. Another study observed a reset of muscle strength when continuation of PRT was prohibited.[25] Yet, it remains to be investigated if the effects of PRT can be maintained beyond 12 weeks when participants are left to self-guided physical activity.

The purpose of the present study was to investigate; (a) if long-term PRT improves functional capacity with concomitant neuromuscular adaptations, and (b) whether improvements can be maintained with self-guided training after 24 weeks of follow-up.

It was hypothesised that long-term PRT would induce pronounced improvements in functional capacity concomitantly with neuromuscular adaptations which would be maintained at follow-up.

Methods

Subjects and design

Thirty-five subjects were recruited from the MS Clinic at Aarhus University Hospital and the MS Clinic of Southern Jutland. Inclusion criteria were; 18–60 years, a definite relapsing–remitting MS diagnosis according to the McDonald criteria, an Expanded Disability Status Scale (EDSS) score[26] of 2.0–5.5 with a 'pyramidal functions' sub-score ≥2, undergoing Interferon (IFN)-β 1a or 1b treatment for at least three months. Exclusion criteria were; co-morbidities preventing participation (cardiovascular disease, metabolic diseases etc.), pregnancy, relapse within an eight-week period prior to inclusion or participation in systematic PRT three months prior to inclusion. Participants gave written informed consent and the study was approved by the ethics committee of Region Midtjylland (M-20110178), and registered at ClinicalTrials.gov (NCT01518660).

Following inclusion and baseline testing, subjects were randomised (stratified for gender) to either a training or waitlist group. Allocation was concealed by the sealed envelope principle. The training group underwent supervised long-term PRT for 24 weeks, while the waitlist group continued their habitual lifestyle without commencing PRT. After 24 weeks, the waitlist group underwent the same PRT intervention, while the initial training group were allowed to continue community-based self-guided training. Testing was performed at baseline (pre), after 24 weeks (post) and after 48 weeks (follow-up) (Figure 1) and each test session was separated at least 48 h from the last exercise bout.

Training protocol

The training intervention consisted of 24 weeks of twice weekly supervised PRT. Training progression followed the general recommendations of the American College of Sports Medicine[27] and the MS specific recommendations from our group.[28] The training protocol is presented in Table 1.

Every session consisted of four lower body exercises (horizontal leg press, hip flexion, leg extension and

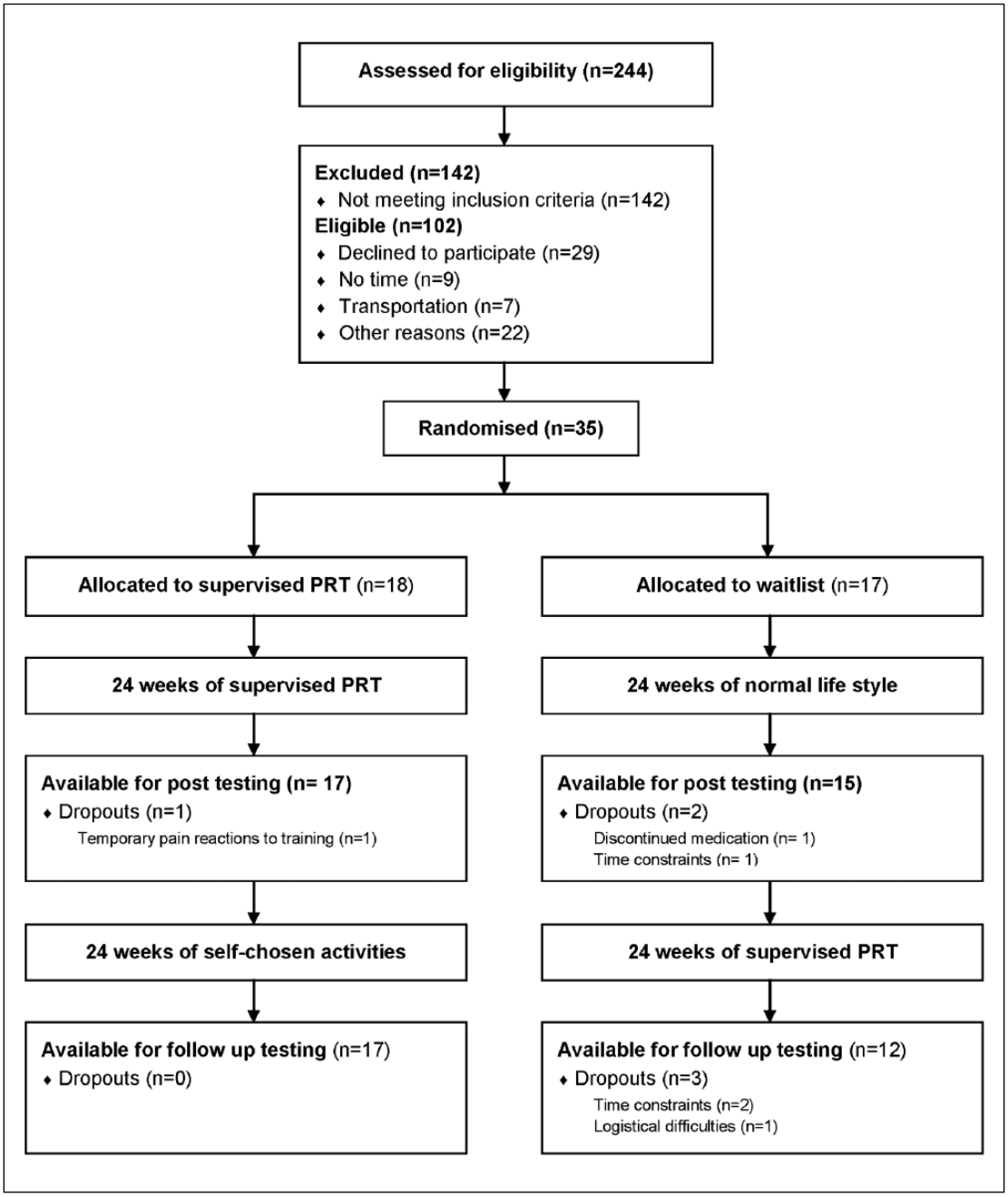

Figure 1. Study flowchart.
PRT: progressive resistance training.

prone hamstring curl) and two upper body exercises (cable pull down and cable triceps extension).

Demographic measures

EDSS scores were assessed by trained neurologists. Weight and fat percentages were determined using a body composition analyser (Tanita SC220, Tanita, Illinois, USA).

Functional capacity

Walking performance was measured as both a short (Timed 25 ft Walk Test (T25FWT)) and a long (Two-Minute Walk Test (2MWT)) walking test.[29] The 5-Time Sit-To-Stand Test (5STS) was performed twice in accordance with Møller et al.[30] Lastly, an ascending stair climb test was performed. Subjects ascended 22 steps (17 cm height, 29 cm depth), with a 180° separating swing half-way, as fast as possible,

Table 1. Training protocol.

Week	Sets	Reps	Intensity	Rest
1–2	3	10	15 RM	2 min
3–4	3	12	15 RM	2 min
5–6	3	10	12 RM	2 min
7–8	4	10	10 RM	2–3 min
9–10	4	8	8 RM	2–3 min
11–12	4	6	6 RM	3 min
13–14	3	10	12 RM	2 min
15–16	4	10	10 RM	2–3 min
17–18	4	10	10 RM	2–3 min
19–20	4	8	8 RM	2–3 min
21–22	4	6	6 RM	3 min
23–24	5	6	6 RM	3 min

Reps: repetitions in each set; RM: repetition maximum.

taking one step at a time without using the rail. For all measures, the best trial was used for further analyses. The assessor of functional capacity was not blinded to the intervention arms.

Additionally, the MSWS-12[24] was completed and transformed to a 0–100 scale.

Isokinetic dynamometry and surface electromyography (EMG)

Protocol. Subjects were seated in an isokinetic dynamometer (Humac Norm, CSMi, Stoughton, Massachusetts, USA) with a hip angle of 90° as described previously.[30] After a standardised instruction (to contract as strongly and fast as possible) and two familiarisation attempts, the subjects performed 3–5 maximal isometric voluntary contractions (MVCs) for the knee extensors and flexors at a knee angle of 70° and 20°, respectively. The subjects received visual feedback and standardised verbal encouragement during each attempt. All contractions were separated by >30 s of rest. Unilateral testing was performed of both legs, and the attempt having the highest peak torque was used for further analysis. The dominant leg was determined as the subject's self-reported best functioning leg at baseline. Concomitantly, surface EMG electrodes (Ambu Blue Sensor N, AMBU, Ballerup, Denmark) were attached to musculi (mm.) vastus lateralis and biceps femoris. After shaving and cleaning the skin, electrodes were placed 2 cm apart and in relation to anatomical marks. The assessor was not blinded to the intervention arms.

Analysis. All data were sampled using TeleMyo Direct Transmission System and MyoResearch Software (Noraxon, Scottsdale, Arizona, USA) at 1500 Hz, and analyses were performed using custom-made software. Torque data were filtered using a Butterworth low-pass filter (cut-off frequency: 6 Hz), and gravity corrected. Contraction onset was defined when torque increased above 7.5 Nm[15] and MVC was defined as the peak torque measurement. Maximal RFD (RFDmax) was defined as the steepest slope between onset and MVC. Additionally, RFD was determined as the average slope from 0–50 ms (RFD@50 ms) and 0–200ms (RFD@200 ms) after onset of contraction.[15] All torque measurements were scaled to body-weight. EMG signals were full-wave rectified and similarly low-pass filtered. Subsequently, area under the curve (integrated EMG; iEMG) from 40 ms before to 10 ms after MVC was calculated. Additionally, the mean frequencies of the neural firing were calculated.

MRI

All imaging was performed with a 1.5-Tesla MRI-scanner (MAGNETOM Avanto, Siemens, Erlangen, Germany). Scans were performed using the spine coil and two anterior coils covering both thighs. After an initial frontal scout scan, a transversal T1-weighted fast spin-echo sequence covering from fossa intercondylaris to caput femoris was applied. The sequence had the following parameters: scan-matrix=448×270, field-of-view=450×271 mm, number of slices=60, slice thickness=7.0 mm, slice gap=3.0 mm, Repetition Time (TR) = 1200 ms, Echo Time (TE)=11 ms, echo train length = 4 and total scan time=4 min 36 s.

The CSA of m. quadriceps (mm. vastus lateralis, medialis, intermedius and rectus femoris) and hamstrings (mm. semitendinosus and semimembranosus and biceps femoris) was determined using OsiriX Software v.4.1.2 (Pixmeo, Bernex, Switzerland). At 50% of femur length (calculated from fossa intercondylaris to caput femoris), a blinded assessor manually tracked the circumference of the muscle compartments (Figure 2) and the software calculated CSA values. All scans were checked for abnormalities by an experienced radiologist.

Statistics

Baseline demographic measures were checked for normality by visual inspection of QQ-plots and histograms and subsequently analysed using Student's *t*-test or non-parametric rank sum tests.

All measures acquired at week 0, 24 and 48 were analysed using a two-way mixed effects analysis of variance (ANOVA) with repeated measures. Intention-to-treat

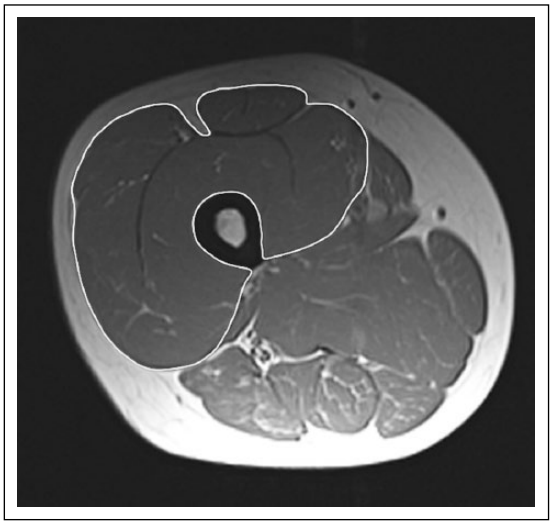

Figure 2. Magnetic Resonance Imaging of thigh. Example of manual circumference tracking of musculus quadriceps.

analysis was applied. Normality was checked by visual inspection of residuals derived from the ANOVA. Whenever a significant two-way interaction between time (week 0, 24 and 48) and group (training and waitlist) was observed, post-hoc linear pairwise comparisons were performed to test within (i.e. change in training group from week 0 to week 24) and between group changes. Additionally, to investigate the coherence of changes in strength and functional capacity, linear regressions were performed for the observed changes after the first 24 weeks.

All statistical analyses were performed in Stata v.13.1 (StataCorp, Texas, USA), and graphs were made using GraphPad Prism v.6.04 (GraphPad Software Inc., California, USA). Statistical significance was set at $p \leq 0.05$.

Results

Subjects

The included subjects had a baseline age, height, weight and fat-percentage of 43.2±8.1 years, 170.4±8.4 cm, 75.3±12.5 kg and 32.2±8.3 %, respectively. Median (range) EDSS score and disease duration were 3 (2–4) and 5 (0.5–28) years, respectively. No baseline between-groups difference was detected. Furthermore, no changes were observed between groups for either weight or fat-percentage (data not shown). In the training group, two subjects suffered from a relapse between week 24 and 48 (after completing the training intervention), but were stable again at week 48, and thus tested and included in the analyses.

The 29 subjects who completed the study participated in (mean±standard deviation (SD)) 44.7±2.2 of 48 sessions, corresponding to 93±5% compliance. Altogether 15 of 17 training group subjects available for follow-up reported continued self-guided (or physiotherapist-assisted) resistance training with lower to similar intensity once or twice weekly.

Functional capacity

The training group significantly improved performance in T25FWT, 2MWT, 5STS, stair climb as well as MSWS-12 score, following PRT (Table 2 and Figure 3). These effects were maintained until follow-up, except for the MSWS-12 score which returned to baseline levels. The waitlist group did not change in any measure during the control period, but showed similar pattern of improvements in performance of the T25FWT, 5STS and stair climb following the 24 weeks PRT from post to follow-up.

Neuromuscular parameters

Knee extensors. MVC increased in both the dominant and non-dominant knee extensors in both groups as a result of 24 weeks PRT (Table 3 and Figure 4). For the training group, the increased MVC was sustained at follow-up. All RFD measures increased after PRT for the training group in the non-dominant leg, but returned to baseline level at follow-up. The waitlist group showed tendencies to similar increases following PRT. No effect was observed for the dominant leg in either group. For the training group an increase in iEMG of m. vastus lateralis in the non-dominant leg was observed after PRT, but was not maintained at follow-up. The waitlist group did not have a significant within group increase in iEMG, but compared to the change in the training group, this was significant. Only the non-dominant m. quadriceps increased CSA as a result of PRT in both groups.

Knee flexors. MVC of the non-dominant leg increased in both groups as a result of PRT, and the training group maintained the improvements until follow-up (Table 4 and Figure 4). RFD@200 and RFDmax similarly increased in the non-dominant leg as a result of training in both groups. For both MVC and all RFD measures the dominant leg did not significantly change throughout the study. M. biceps femoris iEMG increased in both legs for the training group after PRT, but returned to baseline at follow-up. The waitlist group only improved iEMG of the dominant leg following PRT. Hamstring CSA increased in both groups and legs following PRT, but decreased again at follow-up for the training group.

Table 2. Functional capacity before and after progressive resistance training and at follow-up in people with multiple sclerosis (MS).

	Absolute values Mean±SD			Interaction (p-level)	Comparison of changes between groups Mean (95% CI)	
	Pre	Post	Follow-up		Δ (Post–Pre)	Δ (Follow-up–Post)
T25FWT (m/s)						
Training	1.65±0.1	1.82±0.1[a]	1.80±0.1[b]	0.01	−0.16 (−0.27 to −0.05)	(reference)
Waitlist	1.77±0.1	1.77±0.1	1.86±0.1[c,d]		(reference)	−0.11 (−0.23 to 0.05)
2MWT (m/s)						
Training	1.60±0.1	1.78±0.1[a]	1.75±0.1[b]	0.03	−0.14 (−0.25 to −0.03)	(reference)
Waitlist	1.63±0.1	1.67±0.1	1.69±0.1		(reference)	−0.05 (−0.17 to 0.06)
5STS (s)						
Training	10.0±0.6	7.9±0.6[a]	7.4±0.6[b]	<0.01	2.4 (1.3 to 3.5)	(reference)
Waitlist	9.00±0.6	9.3±0.6	7.7±0.6[a,e]		(reference)	1.0 (–0.2 to 2.1)
Stair climb (s)						
Training	11.0±1.8	9.6±1.8[a]	9.9±1.8[e]	<0.01	1.93 (0.8 to 3.1)	(reference)
Waitlist	12.6±1.8	13.1±1.8	12.0±1.8[f]		(reference)	1.4 (0.1 to 2.6)
MSWS-12 (a.u.)						
Training	32.5±5.3	24.0±5.4[f]	31.4±5.4[f]	0.05	7.3 (–2.5 to 17.2)	(reference)
Waitlist	27.2±5.5	26.0±5.6	20.7±5.8[g]		(reference)	12.7 (2.4 to 23.0)

2MWT: 2 Minute Walk Test; 5STS: 5-Time Sit-to-Stand test; CI: confidence interval; MSWS-12: 12-item MS Walking Scale; SD: standard deviation; T25FWT: Timed 25 ft Walk Test; a.u.: arbitrary units.

[a]Significant within group change from previous measurement: $p \leq 0.001$.

[b]Within group follow-up significantly different from pre: $p \leq 0.001$.

[c]Trend ($p<0.1$) to within group change from previous measurement.

[d]Within group follow-up significantly different from pre: $p \leq 0.05$.

[e]Within group follow-up significantly different from pre: $p \leq 0.01$.

[f]Significant within group change from previous measurement: $p \leq 0.05$.

[g]Trend ($p<0.1$) to within group change from pre.

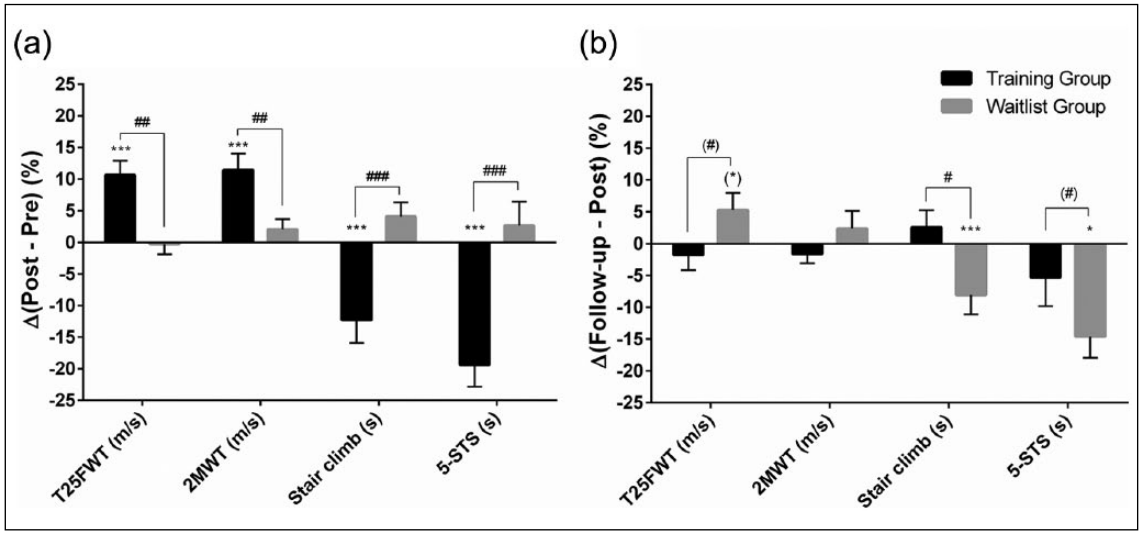

Figure 3. Functional capacity.
Mean (standard error (SE)) percentage change from (a) pre to post and (b) post to follow-up in the training and waitlist group. Within group change: $^{(*)}p<0.1$, $^{*}p<0.05$, $^{***}p<0.001$. Between group difference: $^{(\#)}p<0.1$, $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$. 2MWT: Two-Minute Walk Test; 5-STS: 5-Time Sit-To-Stand; T25FWT: Timed 25 ft Walk Test.

Additional measurements. For either leg, mean firing frequency of mm. vastus lateralis and biceps femoris during knee extension and flexion, respectively, did not show any significant two-way interaction (data not shown).

The linear regressions demonstrated that the changes in T25FWT, 2MWT, 5STS and stair climb test after the first 24 weeks were associated with changes in MVC of both the non-dominant knee extensors and knee flexors (for all regressions, $p<0.01$). For the changes in the dominant leg, similar associations with the changes in functional capacity were observed ($p<0.05$), with the exception of knee extensor MVC and stair climb test ($p=0.11$).

Discussion

The two main findings of the current study were; (a) that improvements in functional capacity are achieved concomitantly with neuromuscular adaptations, when total training volume (i.e. intensity × duration of training period) is of sufficient magnitude; and (b) that training-induced improvements can be maintained for extended periods of time with self-guided non-supervised training. Furthermore, the neuromuscular improvements primarily occurred in the non-dominant leg.

Neuromuscular adaptations

The improvements observed in both knee extensor and flexor muscle strength correspond to, or even exceed, those of previous studies,[6] the latter finding likely relating to the long-term intervention as well as the higher exercise intensity. With regard to RFD of both knee extensors and flexors, this is the first study to demonstrate improvements in RFD as a result of PRT. These improvements are of relevance, since RFD has been proposed to correlate with balance and risk of falls.[12] When considering changes in both iEMG and CSA, the relative neural adaptations correspond to previous observations by Dalgas et al.,[18] suggesting almost complete normalisation of the deficit of PwMS.[13] The training group concomitantly improved CSA of the non-dominant knee extensors and flexors by 2.7% and 5.3%, respectively, which is a relatively modest degree compared to previous studies on PwMS following prolonged PRT.[20] Discrepancies between studies may partly relate to discrepancies between measurements in mean fibre and whole muscle CSA in the knee extensor muscle which are also influenced by fibre pennation angle.[16]

Improvements in functional capacity and clinical importance

Other studies have not consistently demonstrated improvements in functional capacity[8,9] after PRT, which might relate to diverging training duration, intensity or differences in disease severity.[6] The present study utilised higher intensity PRT and, included a prolonged training period compared to previous RCTs.[6] As for the disease severity, this study only included participants with EDSS scores between 2–4,

Table 3. Neuromuscular function for knee extensors before and after progressive resistance training and at follow-up in people with multiple sclerosis (MS).

Measurement	Time	Non-dominant		Interaction	Dominant		Interaction
		Training	Waitlist	(*p*-level)	Training	Waitlist	(*p*-level)
MVC (Nm/kg)	Pre	2.11±0.14	1.94±0.15	<0.01	2.28±0.16	2.17±0.16	<0.01
	Post	2.48±0.14[a]	1.99±0.15		2.64±0.16[a]	2.23±0.16	
	Follow-up	2.36±0.14[b]	2.37±0.16[a,c]		2.49±0.16[d]	2.54±0.17[b,e]	
	Δ (Post–Pre)	−0.31 (−0.58 to −0.04)	(reference)		−0.31 (−0.61 to −0.02)	(reference)	
	Δ (Follow-up–Post)	(reference)	−0.49 (−0.78 to −0.21)		(reference)	−0.47 (−0.78 to −0.16)	
RFD@50 ms (Nm/kg/s)	Pre	9.92±0.77	9.97±0.79	0.04	10.50±0.85	10.37±0.88	0.46
	Post	11.40±0.78[f]	9.03±0.82		10.32±0.87	10.90±0.92	
	Follow-up	10.39±0.78	10.42±0.89[g]		10.80±0.89	9.76±0.99	
	Δ (Post–Pre)	−2.42 (−4.51 to −0.33)	(reference)		non-significant		
	Δ (Follow-up–Post)	(reference)	−2.40 (−4.60 to −0.20)				
RFD@200 ms (Nm/kg/s)	Pre	6.79±0.56	6.42±0.58	0.06[h]	7.29±0.58	7.07±0.60	0.80
	Post	7.71±0.57[f]	6.05±0.60		7.73±0.59	7.23±0.62	
	Follow-up	7.38±0.57	7.16±0.63[f]		7.87±0.60	7.21±0.65	
	Δ (Post–Pre)	−1.29 (−2.58 to 0.00)	(reference)		non-significant		
	Δ (Follow-up–Post)	(reference)	−1.44 (−2.80 to −0.08)				
RFDmax (Nm/kg/s)	Pre	12.84±0.75	12.56±0.77	0.05	13.13±0.75	13.34±0.77	0.83
	Post	14.19±0.76[f]	12.11±0.80		13.65±0.76	13.29±0.80	
	Follow-up	13.12±0.76[g]	13.16±0.85		13.18±0.77	13.15±0.85	
	Δ (Post–Pre)	−1.79 (−3.58 to −0.02)	(reference)		non-significant		
	Δ (Follow-up–Post)	(reference)	−2.11 (−3.99 to −0.23)				
VL iEMG (μV)	Pre	8.29±1.04	7.98±1.07	0.09[h]	10.12±1.25	9.38±1.29	0.05
	Post	10.00±1.05[f]	8.01±1.10		10.53±1.27	8.82±1.33	
	Follow-up	8.97±1.05	9.20±1.14		8.66±1.29[g]	10.70±1.41	
	Δ (Post–Pre)	−1.68 (−3.66 to 0.30)	(reference)		−0.97 (−3.88 to 1.94)	(reference)	
	Δ (Follow-up–Post)	(reference)	−2.21 (−4.31 to −0.13)		(reference)	−3.75 (−6.85 to −0.66)	
CSA quadriceps (cm²)	Pre	56.3±2.73	56.2±2.81	0.06[h]	58.2±3.17	58.7±3.26	0.46
	Post	57.7±2.73[f]	57.1±2.82		59.1±3.17	59.2±3.27	
	Follow-up	57.0±2.73	58.6±2.84[b,f]		59.4±3.17	60.7±3.28	
	Δ (Post–Pre)	−0.54 (−2.40 to 1.32)	(reference)		non-significant		
	Δ (Follow-up–Post)	(reference)	−2.26 (−4.21 to −0.31)				

CSA: cross-sectional area; iEMG: integrated electromyography; MVC: maximal voluntary contraction; RFD: rate of force development; VL: vastus lateralis.
Absolute values are mean±standard deviation. Differences in changes are mean (95% confidence interval).
[a]Significant within group change from previous measurement: $p \leq 0.001$. [b]Within group follow-up significantly different from pre: $p \leq 0.01$.[c]Within group follow-up significantly different from pre: $p \leq 0.001$. [d]Within group follow-up significantly different from pre: $p \leq 0.05$. [e]Significant within group change from previous measurement: $p \leq 0.01$. [f]Significant within group change from previous measurement: $p \leq 0.05$. [g]Trend ($p < 0.1$) to within group change from previous measurement. [h]Trend ($p < 0.1$) for two-way interaction and post-hoc tests performed.

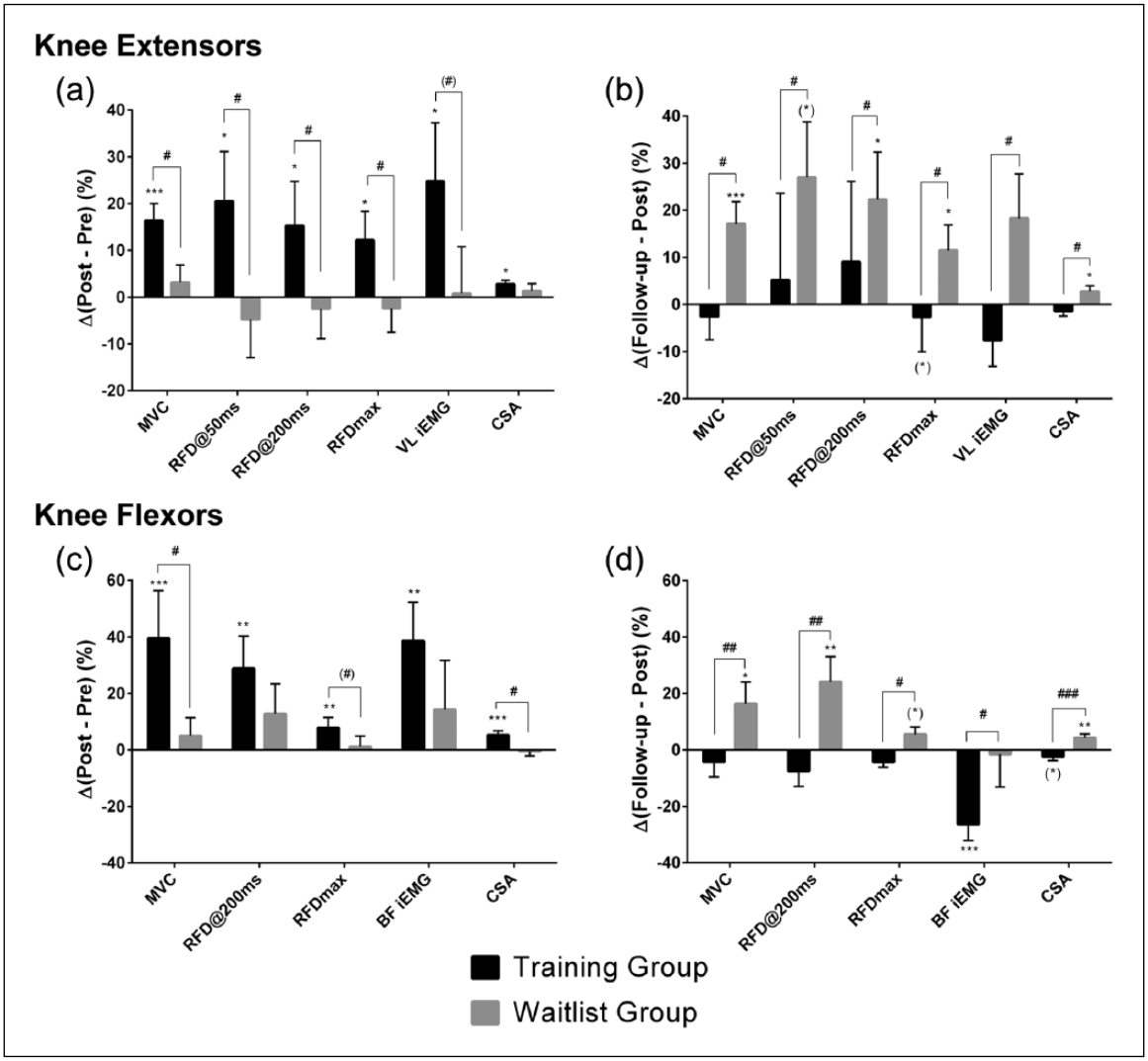

Figure 4. Relative change for the knee extensors ((a) and (b)) and flexors ((c) and (d)) of the non-dominant leg.
Mean (standard error (SE)) percentage change in neuromuscular parameters from pre to post ((a) and (c)) and post to follow-up ((b) and (d)) in knee extensors and flexors of the training and waitlist group. Within group change: $^{(*)}p<0.1$, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$. Between group difference: $^{(\#)}p<0.1$, $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$. BF: biceps femoris; CSA: cross-sectional area; iEMG: integrated electromyography; MVC: maximal voluntary contraction; RFD: rate of force development; VL: vastus lateralis.

with all participants having a 'pyramidal functions' sub-score ≥2, ensuring baseline disability.[26]

Despite the compelling improvements in functional capacity, not all measures reached magnitudes considered clinically important. Accordingly, whereas the 2MWT (+0.18 m/s corresponding to 21.6 m) showed clinically meaningful improvements according to Baert et al.[23], the MSWS-12 (–8.5 points) only fulfilled the criteria for clinical improvement according to some[31] but not all[23] threshold definitions. Regarding the T25FWT, a 20% change has been suggested as both a clinical meaningful change[32] and the minimal reliable change,[33] which was not achieved in this study. Thresholds of clinical meaningful change of the 5STS are unknown, but studies of day-to-day variability suggest variation corresponding to the T25FWT,[30] indicating that the improvement in the training group of –19.4% at least approaches a reliable change. Of interest is the apparent incoherence of the MSWS-12 and the objective measures of functional capacity during the follow-up period in the training group. This suggests that MSWS-12 might be influenced by other parameters, such as balance, not directly reflected by either of our other measures of functional capacity.

Follow-up and reproducibility

Only Dalgas et al.[7] have previously included a follow up period after PRT and shown maintenance of

Table 4. Neuromuscular function for knee flexors before and after progressive resistance training and at follow-up in people with multiple sclerosis (MS).

Measurement>	Time	Non-dominant		Interaction	Dominant		Interaction
		Training	Waitlist	(*p*-level)	Training	Waitlist	(*p*-level)
MVC (Nm/kg)	Pre	0.82±0.09	0.85±0.09	0.02	0.89±0.08	0.94±0.09	0.31
	Post	1.08±0.09[a]	0.91±0.10		1.03±0.08	0.98±0.09	
	Follow-up	0.98±0.09[b]	1.08±0.10[c,d]		1.05±0.09	1.13±0.09	
	Δ (Post–Pre)	−0.18 (−0.35 to −0.01)	(reference)		non-significant		
	Δ (Follow-up–Post)	(reference)	−0.25 (−0.43 to −0.07)				
RFD@50 ms (Nm/kg/s)	Pre	4.46±0.33	4.15±0.34	0.17	4.41±0.31	4.90±0.32	0.17
	Post	5.28±0.34	4.53±0.36		4.67±0.32	4.74±0.34	
	Follow-up	4.90±0.34	5.12±0.39		4.95±0.33	4.57±0.36	
	Δ (Post–Pre)	non-significant			non-significant		
	Δ (Follow-up–Post)						
RFD@200 ms (Nm/kg/s)	Pre	2.62±0.27	2.40±0.27	<0.01	2.67±0.25	2.88±0.26	0.55
	Post	3.23±0.27[e]	2.58±0.28		2.90±0.25	2.72±0.27	
	Follow-up	2.89±0.27	3.27±0.30 [d,e]		3.14±0.26	3.17±0.28	
	Δ (Post–Pre)	−0.43 (−1.03 to 0.17)	(reference)		non-significant		
	Δ (Follow-up–Post)	(reference)	−1.02 (−1.65 to −0.38)				
RFDmax (Nm/kg/s)	Pre	8.32±0.35	8.01±0.36	0.05	8.27±0.35	8.33±0.36	0.21
	Post	9.00±0.35[e]	8.04±0.37		8.36±0.35	8.29±0.37	
	Follow-up	8.57±0.35[f]	8.53±0.39[f,g]		8.70±0.36	8.11±0.39	
	Δ (Post–Pre)	−0.65 (−1.36 to 0.07)	(reference)		non-significant		
	Δ (Follow-up–Post)	(reference)	−0.92 (−1.67 to −0.16)				
BF iEMG (μV)	Pre	9.98±1.44	10.11±1.49	0.07[h]	9.65±1.58	9.43±1.62	0.04
	Post	13.25±1.47[e]	10.47±1.54		13.30±1.61[c]	11.00±1.69	
	Follow-up	8.99±1.47[a]	10.37±1.64		10.01±1.64	13.63±1.82[c,i]	
	Δ (Post–Pre)	−2.91 (−6.46 to 0.63)	(reference)		−2.09 (−6.36 to 2.18)	(reference)	
	Δ (Follow-up–Post)	(reference)	−4.16 (−7.90 to −0.43)		(reference)	−5.93 (−10.48 to −1.39)	
CSA hamstrings (cm^2)	Pre	25.0±1.22	27.2±1.26	<0.01	25.4±1.39	25.9±1.43	<0.01
	Post	26.4±1.23[a]	27.2±1.27		26.5±1.39[e]	26.9±1.44	
	Follow-up	25.8±1.23[f,g]	28.5±1.28[b,e]		25.6±1.39[c]	28.6±1.45[a,d]	
	Δ (Post–Pre)	−1.31 (−2.36 to −0.26)	(reference)		−1.20 (−2.33 to −0.07)	(reference)	
	Δ (Follow-up–Post)	(reference)	−1.92 (−3.02 to −0.82)		(reference)	−2.62 (−3.81 to −1.43)	

BF: biceps femoris; CSA: cross-sectional area; iEMG: integrated electromyography; MVC: maximal voluntary contraction; RFD: rate of force development.
Absolute values are mean±standard deviation. Differences in changes are mean (95% confidence interval).
[a]Significant within group change from previous measurement: $p \leq 0.001$. [b]Within group follow-up significantly different from pre: $p \leq 0.01$. [c]Significant within group change from previous measurement: $p \leq 0.05$. [d]Within group follow-up significantly different from pre: $p \leq 0.001$. [e]Significant within group change from previous measurement: $p \leq 0.01$. [f]Trend ($p < 0.1$) to within group change from previous measurement. [g]Trend ($p < 0.1$) to within group change from pre. [h]Trend ($p < 0.1$) for two-way interaction and post-hoc tests performed. [i]Within group follow-up significantly different from pre: $p \leq 0.05$.

improvements achieved in the supervised phase. Other studies have reported improvements in functional capacity[34] and self-directed exercise behaviour[35] after different supervised exercise interventions, but observed regression to baseline levels at follow-up. In our study, 15/17 completers in the training group reported a continuation of self-guided resistance training in a community-based setting. The overall interpretation at follow-up was maintenance of the improvements attained during the supervised PRT. As observed by Dalgas et al.,[7] the waitlist group overall showed a similar, but less compelling, pattern of improvements compared to the initial training group. We have no clear explanation for this, but this could be due to disease progression limiting training adaptability and/or motivational issues caused by the waitlist design.

Dominant versus non-dominant leg

One interesting observation of the current study comprised the seemingly clearer pattern of neuromuscular improvements in the non-dominant compared to the dominant leg. Although, MVC of both non-dominant and dominant knee extensors increased to a similar extent in the training group (16.4% vs 15.6%, respectively), only the non-dominant leg improved RFD, iEMG and CSA. For the knee flexors, only the non-dominant leg improved MVC significantly for the training group (39.6%), although a non-significant change of 14.5% was observed in the dominant leg, which can be explained by statistically similar changes observed for iEMG (38.6% vs 34.6%) and CSA (5.3% vs 4.2%). Again, only the non-dominant leg improved in the measures of RFD.

Likely, the unilateral exercises in the present study caused a greater stress on the non-dominant leg which, combined with the lower baseline values of the neuromuscular parameters, caused larger relative improvements. Importantly, earlier cross-sectional studies have demonstrated that functional capacity correlates better with the weakest leg,[5] suggesting that adaptations here is of great importance for the translation to improved functional capacity.

Limitations

Limitations of the present study include lack of blinding of participants and most assessors and the quite narrow MS population included which may compromise generalisability of the results.

Another limitation in relation to the present study is the acquired sample size. As stated in the registration at clinicaltrials.gov, the primary purpose of the present study was to investigate immunological responses to PRT (not published yet), and the study was powered accordingly. However, a previous study[7] demonstrates that the present study is of sufficient size to detect changes in muscle strength. Additionally, the present study presents the results of several statistical tests, which increases the likelihood of statistical type I errors. The current study had six dropouts, mainly from the waitlist group, because of changed priorities causing lack of time to participate in the PRT intervention when eventually offered. The dropout rate corresponding to 17% is greater than other studies,[6] but is believed to be a consequence of the long-term study design.

Conclusion

In conclusion the present study showed that (a) high volume PRT efficiently improves functional capacity with concomitant neuromuscular adaptations in mild to moderately impaired PwMS; (b) improvements can be maintained for extended periods of time with community-based self-guided physical activity, and (c); neuromuscular adaptation are generally more pronounced in the non-dominant leg.

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Conflict of interest

The authors declare that there is no conflict of interest.

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References

1. Compston A and Coles A. Multiple sclerosis. *Lancet* 2008; 372: 1502–1517.
2. Heesen C, Bohm J, Reich C, et al. Patient perception of bodily functions in multiple sclerosis: Gait and visual function are the most valuable. *Mult Scler* 2008; 14: 988–991.
3. Jensen HB, Ravnborg M, Dalgas U, et al. 4-Aminopyridine for symptomatic treatment of multiple sclerosis: A systematic review. *Ther Adv Neurol Disord* 2014; 7: 97–113.

4. Schwid SR, Thornton CA, Pandya S, et al. Quantitative assessment of motor fatigue and strength in MS. *Neurology* 1999; 53: 743–750.
5. Broekmans T, Gijbels D, Eijnde BO, et al. The relationship between upper leg muscle strength and walking capacity in persons with multiple sclerosis. *Mult Scler* 2013; 19: 112–119.
6. Kjolhede T, Vissing K and Dalgas U. Multiple sclerosis and progressive resistance training: A systematic review. *Mult Scler* 2012; 18: 1215–1228.
7. Dalgas U, Stenager E, Jakobsen J, et al. Resistance training improves muscle strength and functional capacity in multiple sclerosis. *Neurology* 2009; 73: 1478–1484.
8. Broekmans T, Roelants M, Feys P, et al. Effects of long-term resistance training and simultaneous electro-stimulation on muscle strength and functional mobility in multiple sclerosis. *Mult Scler* 2011; 17: 468–477.
9. Dodd K, Taylor N, Shields N, et al. Progressive resistance training did not improve walking but can improve muscle performance, quality of life and fatigue in adults with multiple sclerosis: A randomized controlled trial. *Mult Scler* 2011; 17: 1362–1374.
10. Chen WY, Pierson FM and Burnett CN. Force-time measurements of knee muscle functions of subjects with multiple sclerosis. *Phys Ther* 1987; 67: 934–940.
11. Ng AV, Miller RG, Gelinas D, et al. Functional relationships of central and peripheral muscle alterations in multiple sclerosis. *Muscle Nerve* 2004; 29: 843–852.
12. Aagaard P. Training-induced changes in neural function. *Exerc Sport Sci Rev* 2003; 31: 61–67.
13. Scott SM, Hughes AR, Galloway SD, et al. Surface EMG characteristics of people with multiple sclerosis during static contractions of the knee extensors. *Clin Physiol Funct Imaging* 2011; 31: 11–17.
14. Garner DJ and Widrick JJ. Cross-bridge mechanisms of muscle weakness in multiple sclerosis. *Muscle Nerve* 2003; 27: 456–464.
15. Aagaard P, Simonsen EB, Andersen JL, et al. Increased rate of force development and neural drive of human skeletal muscle following resistance training. *J Appl Physiol* 2002; 93: 1318–1326.
16. Folland JP and Williams AG. The adaptations to strength training: Morphological and neurological contributions to increased strength. *Sports Med* 2007; 37: 145–168.
17. Fimland MS, Helgerud J, Gruber M, et al. Enhanced neural drive after maximal strength training in multiple sclerosis patients. *Eur J Appl Physiol* 2010; 110: 435–443.
18. Dalgas U, Stenager E, Lund C, et al. Neural drive increases following resistance training in patients with multiple sclerosis. *Journal of Neurology* 2013; 260:1822–1832.
19. White LJ, McCoy SC, Castellano V, et al. Resistance training improves strength and functional capacity in persons with multiple sclerosis. *Mult Scler* 2004; 10: 668–674.
20. Dalgas U, Stenager E, Jakobsen J, et al. Muscle fiber size increases following resistance training in multiple sclerosis. *Mult Scler* 2010; 16: 1367–1376.
21. De Souza-Teixeira F, Costilla S, Ayan C, et al. Effects of resistance training in multiple sclerosis. *Int J Sports Med* 2009; 30: 245–250.
22. Kieseier BC and Pozzilli C. Assessing walking disability in multiple sclerosis. *Mult Scler* 2012; 18: 914–924.
23. Baert I, Freeman J, Smedal T, et al. Responsiveness and clinically meaningful improvement, according to disability level, of five walking measures after rehabilitation in multiple sclerosis: a European multicenter study. *Neurorehabilitation and Neural Repair*. 2014; 28: 621–631.
24. Hobart JC, Riazi A, Lamping DL, et al. Measuring the impact of MS on walking ability: The 12-Item MS Walking Scale (MSWS-12). *Neurology* 2003 ; 60: 31–6.
25. Medina-Perez C, de Souza-Teixeira F, Fernandez-Gonzalo R and de Paz-Fernandez JA. Effects of a resistance training program and subsequent detraining on muscle strength and muscle power in multiple sclerosis patients. *NeuroRehabilitation*. 2014; 34: 523–530.
26. Kurtzke JF. Rating neurologic impairment in multiple sclerosis – an Expanded Disability Status Scale (EDSS). *Neurology* 1983; 33: 1444–1452.
27. American College of Sports M. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2009; 41: 687–708.
28. Dalgas U, Stenager E and Ingemann-Hansen T. Multiple sclerosis and physical exercise: Recommendations for the application of resistance-, endurance- and combined training. *Mult Scler* 2008; 14: 35–53.
29. Gijbels D, Dalgas U, Romberg A, et al. Which walking capacity tests to use in multiple sclerosis? A

multicentre study providing the basis for a core set. *Mult Scler* 2012; 18: 364–371.

30. Moller AB, Bibby BM, Skjerbaek AG, et al. Validity and variability of the 5-repetition sit-to-stand test in patients with multiple sclerosis. *Disabil Rehabil* 2012; 34: 2251–2258.
31. Hobart J, Blight AR, Goodman A, et al. Timed 25-foot walk: Direct evidence that improving 20% or greater is clinically meaningful in MS. *Neurology* 2013; 80: 1509–1517.
32. Phan-Ba R, Pace A, Calay P, et al. Comparison of the timed 25-foot and the 100-meter walk as performance measures in multiple sclerosis. *Neurorehabil Neural Repair* 2011; 25: 672–679.
33. Schwid SR, Goodman AD, McDermott MP, et al. Quantitative functional measures in MS: What is a reliable change? *Neurology* 2002; 58: 1294–1296.
34. Garrett M, Hogan N, Larkin A, et al. Exercise in the community for people with multiple sclerosis–a follow-up of people with minimal gait impairment. *Mult Scler* 2013; 19: 790–798.
35. Carter A, Daley A, Humphreys L, et al. Pragmatic intervention for increasing self-directed exercise behaviour and improving important health outcomes in people with multiple sclerosis: a randomised controlled trial. *Multiple Sclerosis*. 2014; 20: 1112–1122.

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