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Callesen, Jacob Lynge; Brincks, John; Cattaneo, Davide; Dalgas , Ulrik

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How does strength training and balance training affect gait and fatigue in patients with Multiple Sclerosis? A study protocol of a randomized controlled trial

Jacob Callesen\textsuperscript{a,b,*}, Davide Cattaneo\textsuperscript{c}, John Brincks\textsuperscript{a} and Ulrik Dalgas\textsuperscript{b}
\textsuperscript{a}Department of Physiotherapy, VIA University College, Faculty of Health Science, Aarhus, Denmark
\textsuperscript{b}Department of Public Health, Aarhus University, Section of Sport Science, Aarhus, Denmark
\textsuperscript{c}Larice Lab, Don Gnocchi Foundation, Gait and Balance rehabilitation Lab, Milan, Italy

Abstract
INTRODUCTION: Multiple sclerosis (MS) is characterized by a demyelination that results in reduced conductivity in the somatosensory nervous system, decreased muscle strength, vestibular alteration, and severe fatigue. Progressive resistance training (PRT) has proven to be a promising intervention showing a positive effect on muscle strength. Another promising intervention frequently used in neuro-rehabilitation is task specific training where also Balance and Motor Control Training (BMCT) are incorporated. Interestingly, the principles of BMCT do fundamentally contrast the principles of PRT in terms of variation in movement pattern, loading and repetitions. Consequently, knowledge of any diverse effect would be of clinical relevance.

AIM: To evaluate the effects of PRT and BMCT on gait, balance and fatigue in persons with MS.

METHOD: A three-armed multi-center, single-blinded cluster randomized controlled trial with two intervention groups (1. PRT of the lower extremities. 2. BMCT that challenges gait function) and a control group that receives usual care while on a waitlist for a combined PRT + BMCT intervention performed after the two interventions groups have completed their interventions. The interventions last ten weeks with two sessions per week, in groups of 3–6 participants. Number of participants is 30 per intervention – 90 in total. Primary outcome measures for gait function are the Timed 25 Foot Walk (T25FW) and the Six Spot Step Test (SSST). Secondary outcomes are fatigue, perceived gait function, temporo-spatial gait characteristics, balance and strength.

Inclusion criteria are: EDSS 2–6, SSST >8 sec and T25FW >5 sec. Exclusion: Recent attacks and ongoing intensive rehabilitation.

ANALYSIS: The effects in the three groups are examined in a mixed effects regression analysis with group and time as fixed effects and center and patient within center as random effects. Spearman or Pearson correlation analysis will be conducted on baseline data to determine associations between the primary outcomes on gait function and the secondary outcomes on fatigue, spatial gait parameters, balance and patient reported measures.

TRIAL REGISTRATION: The study is approved by the Regional ethical committee and registered at clinicaltrials.gov, NCT02870023.

Keywords: Resistance training, balance training, multiple sclerosis, physiotherapy, gait

\textsuperscript{*} Address for correspondence: Jacob Callesen, Department of Physiotherapy, VIA University College, Faculty of Health Science, Hedeager 2, 8200 Aarhus N, Denmark. Tel.: +45 87552330; E-mail: jacc@via.dk.
1. Background

Multiple sclerosis (MS) is characterized by demyelination of the sensory and motor axons in the central nervous system. MS mostly affects women (women:men ratio: 2–4:1) in the second or third decade of life (Cameron & Wagner, 2011; Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000), and approximately 2.3 million people have the disease worldwide (Multiple Sclerosis International Federation, 2014). The MS disease course is either characterized by stable phases interrupted by periods of disease activity (relapsing-remitting MS), or by a continuous progressive development (primary and secondary progressive MS).

People with MS experience a wide variety of symptoms including impaired muscle strength and balance, fatigue, impaired cognition, depression and spasticity (Cameron & Wagner, 2011). Of these, impaired balance (Boes et al., 2012) and severe fatigue (Claro-Salinas et al., 2013) are described as two of the most debilitating symptoms leading to limitations in activities such as upright posture and gait (Heesen et al., 2008; Penner et al., 2007). Generally, pharmacological symptomatic treatment has not proven efficient in the treatment of balance problems, fatigue and walking impairments, with the exception that Fampridine has beneficial effects on gait performance in a subgroup of patients (Lee, Newell, Ziegler, & Topping, 2008). Consequently, non-pharmacological interventions that effectively target these symptoms are warranted.

In the last decade progressive resistance training (PRT) has proven to be one of the promising interventions in patients with MS showing a consistent and positive effect on muscle strength (Kjolhede, Vissing, & Dalgas, 2012). However, the effect of PRT on functional outcomes are heterogeneous but with promising effects on daily activities such as walking and chair rise (Kjolhede et al., 2012; Latimer-Cheung et al., 2013; Moff & Pilutti, 2012). The evidence for a beneficial effect of PRT on balance and postural control is divergent and yet inadequately investigated (Kjolhede et al., 2012). Regarding fatigue, a recent Cochrane review reported that one could expect improvements in MS fatigue after exercise interventions, despite methodological flaws in the existing literature, but only few studies evaluating PRT were located (Heine, van de Port, Rietberg, van Wegen, & Kwakkel, 2015).

Another promising intervention is task specific training of motor function that is widely used by physiotherapists in neurorehabilitation (Carr & Shepherd, 2010). In this study protocol, motor function is limited to gait related functions with a particular focus put on balance and motor control, why the term Balance and Motor Control Training (BMCT) is applied. There is no universally accepted definition of human balance, but balance defined as “the inherent ability of a person to maintain, achieve or restore a specific state of balance and not to fall, with reference to the motor and sensory systems and to the physical properties of the person” (Pollock, Durward, Rowe, & Paul, 2000), is applied in this study.

Effects obtained from BMCT partly result from plastic changes in the nervous system (Khan, Amatya, Galea, Gonzenbach, & Kesselering, 2016). To induce such effects, repetition of a simple task only has limited efficiency in order to improve performance. Once a task has been learned to a certain level, further practice of the same task will not be accompanied by further induction of plasticity and little is therefore gained by continued practice of the task (Nielsen, Willerslev-Olsen, Christiansen, Lundbye-Jensen, & Lorentzen, 2015). To provide challenges that ensures continued learning, training exercises have to progress from simple movement trajectories to more complex movements, that also incorporates goal setting (Nielsen et al., 2015). Moreover, it has been shown that shaping and variation of tasks in combination with feedback on movement quality is of great importance for the learning outcome (Homberg, 2013). The underlying concept for performing BMCT is, therefore, that improved motor control will optimize the movement strategy, which further leads to improved gait function (Carling, Forsberg, Gunnarsson, & Nilsson, 2016).

Regarding the effects of BMCT on fatigue, there are diverging results in the literature, but the literature on BMCT for patients with MS is generally of low quality with an inadequate description of interventions (Paltamaa, Sjogren, Peurala, & Heinonen, 2012; Rietberg, Brooks, Uitdehaag, & Kwakkel, 2005), why further studies are warranted.

Interestingly, the principles of task specific training do fundamentally contrast the principles of PRT, that normally consist of monotonous movement patterns performed under heavy loading for a low number of repetitions (American College of Sports Medicine, 2009). Consequently, studies comparing the effects of BMCT and PRT on gait function would add to the current literature as no studies doing so could be located. Such a comparison would help clarify whether potential effects are overlapping or differentiated.
and would help guiding future rehabilitation interventions in persons with MS.

The primary objective of this study is, therefore, to investigate and compare the effects of 10 weeks of PRT to BMCT on gait function, balance and fatigue in mobility limited persons with MS.

It is hypothesized that PRT will be superior in improving maximal straight gait speed, whereas BMCT will have a greater impact on balance, fatigue, and more complex walking tasks that include elements of balance and coordination.

2. Methods/design

2.1. Study design

As depicted in Fig. 1, the study is a three-armed multi-center, single-blinded cluster randomized controlled trial with two intervention groups (1: PRT; 2: BMCT) and a control group that receives usual care while on a waitlist followed by an intervention combining PRT and BMCT. Both interventions last ten weeks with two sessions per week.

The study protocol conforms to the SPIRIT statement and is registered at www.clinicaltrials.gov (NCT02870023). The study will be performed in agreement with the Declaration of Helsinki and is approved by the Regional ethical committee (Videnskabsetisk Komite, Region Midt; ID-number: 1-10-72-316-15).

2.2. Recruitment and eligibility

Patients will be invited via regional MS Clinics in the western part of Denmark. Invitations will be provided at consultations at the clinics or will be sent to patients from the registers at the participating MS clinics. Invitations will also be distributed via social media and network groups established via the Danish MS Society.

Patients that reply to an invitation will afterwards receive a detailed written information along with a leaflet from the National ethical committee.

Fig. 1. Illustration of study design.
Eligibility according to inclusion criteria 1–4 (see below) are determined by a neurologist from either medical records or from a consultation in case of insufficient medical record information.

Inclusion criteria are: 1) Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) 2.0–6.0 ($\geq$ 2.0 in the functional system "pyramidal function"); 2) Age >18; 3) Able to walk 100 m; 4) Able to manage own transportation to weekly training sessions as well as to pre- and post-testing; 5) Six Spot Step Test >8 sec; and 6) Timed 25 Foot walk >5 sec.

Exclusion criteria are: 1) Co-morbidity in terms of cognitive disorders or alcohol abuse; 2) Attack within the last eight weeks; 3) Systematic intensive rehabilitation/training within the last three months; 4) Adjustment in medication within 2 months before inclusion (applies for medication that has a disease modifying effect and/or affects gait performance and spasticity).

Interventions will be carried out at physiotherapy clinics located in the community. For a clinic to participate it is required that: 1) the responsible staff in charge of the interventions are experienced in MS rehabilitation; 2) the clinic has a gym facility that enables 10 meter of straight walking as well as contain sufficient balance accessories and equipment for PRT of the lower extremities.

2.3. Random allocation procedures

Group allocation will be determined by cluster randomization with a concealed allocation. The participating clinics are randomly assigned to perform either PRT, BMCT or Control (and later PRT + BMCT). To ensure an even distribution of patients in the intervention groups, allocation is carried out whenever three groups of 3–6 patients are enrolled. Three concealed envelopes, each containing the name of one intervention, is randomly drawn and allocated to a group/clinic. As the patients will be assigned to a clinic located close to their home, the allocation depends on their residential location. A person with no further involvement in the study manages the randomized allocation.

An assistant in charge of the test logistics will assign patients with an ID number and pseudonyms that will be used during baseline- and follow-up testing. This procedure is carried out to avoid that the primary investigator recognizes patients by their names, which are used during the recruitment procedure, where the primary investigator is involved. This way the primary investigator can remain blinded to patient exposure and thus serve as blinded assessor. Patients will be informed about the purpose and the procedures regarding blinding. Identities will be concealed from the primary investigator until data collection is complete.

3. Study flow

Patients that fulfil the inclusion criteria 1–4 will be baseline tested by the primary investigator at Section of Sport Science, Dep. Public Health, Aarhus University. Final allocation to an intervention depends on the result of the baseline scores for the two primary outcome measures (SSST & T25FW). If the scores fall below the predefined limit mentioned in inclusion criteria 5 or 6, patients are not enrolled in the study. Results from all baseline testing (including those who are not enrolled in the study) will be recorded and used in a secondary cross sectional analysis evaluating baseline associations.

When groups are formed and assigned to an intervention, 10 weeks of either BMCT, PRT or Control intervention will begin. Hereafter a follow-up test identical to the baseline test procedure will be carried out. After the intervention period, the control group start their training consisting of combined PRT and BMCT for 10 weeks followed by a third identical test round (Fig. 1).

3.1. Intervention procedures

3.1.1. PRT

Training sessions starts with a 10-minute warm-up on a stationary bicycle or treadmill. All exercises will be performed in machines, sitting, lying or standing adequately supported (Table 1). Variation in exercise equipment in terms of brand and types of machines across the different participating physiotherapy clinics is acceptable as long as the execution of exercises complies with the description (Table 1). Training is supervised by a physiotherapist to ensure high quality during execution and that the intended progressive overload model is followed (Table 2).

3.1.2. BMCT

Each training session starts with a 10-minute warm-up on a stationary bicycle or treadmill.

The BMCT intervention consists of stations with exercises that challenges functions related to mobility. The stations aim at standing, stepping, walking,
Table 1
Description of exercises in the Progressive Resistance Training intervention

<table>
<thead>
<tr>
<th>Exercises</th>
<th>Start position</th>
<th>End position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg press</td>
<td>Sitting or supine</td>
<td>– Plantar flexion</td>
</tr>
<tr>
<td>– using both legs</td>
<td>– Dorsal flexion in ankle</td>
<td>– Extension in knee and hip</td>
</tr>
<tr>
<td>– Flexion in knee and hip</td>
<td>– Mid-range knee flexion</td>
<td>– Full extension</td>
</tr>
<tr>
<td>Knee extension</td>
<td>Sitting</td>
<td>– Full flexion</td>
</tr>
<tr>
<td>– Flexion in knee and hip</td>
<td>– Full flexion</td>
<td>– Full flexion</td>
</tr>
<tr>
<td>Hip flexion</td>
<td>Standing</td>
<td>– Full flexion</td>
</tr>
<tr>
<td>– Slight hip extension</td>
<td>– Full flexion</td>
<td>– Full flexion</td>
</tr>
<tr>
<td>Hamstring curl</td>
<td>Prone</td>
<td>– Full flexion</td>
</tr>
<tr>
<td>– Slight knee flexion</td>
<td>– Full flexion</td>
<td>– Full flexion</td>
</tr>
<tr>
<td>Hip extension</td>
<td>Standing</td>
<td>– Full flexion</td>
</tr>
<tr>
<td>– Mid-range hip flexion</td>
<td>– Full extension</td>
<td>– Full extension</td>
</tr>
</tbody>
</table>

Table 2
Progression model for the PRT intervention

<table>
<thead>
<tr>
<th>Week</th>
<th>Sets</th>
<th>Repetitions</th>
<th>Load in RM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &amp; 2</td>
<td>3</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>3 &amp; 4</td>
<td>3</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>5 &amp; 6</td>
<td>4</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>7 &amp; 8</td>
<td>4</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>9 &amp; 10</td>
<td>4</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

RM = Repetitions Maximum.

sit to stand, and vestibular rehabilitation through gaze control. A detailed framework of the balance intervention is illustrated in appendix 1.

Balance skill is interpreted from the ability to perform the exercises while keeping center of mass (COM) in control within the base of support (BOS). Multiple failed attempts are interpreted as “an inadequate balance for the given task”. Reduced speed, abnormal fluctuating displacement of COM, excessive corrective upper limb movement and a high level of concentration with cessation of talking and head movement is interpreted as “balance being challenged by the given task”. The exercises are progressed by altering BOS, loads and speed during movements, body and/or head turns, and by using external tasks (e.g. catching and throwing). The BMCT framework is defined under inspiration from already published treatment programs by Coote et al. (Coote, Garrett, Hogan, Larkin, & Saunders, 2009), Hebert et al. (Hebert, Corboy, Manago, & Schenkm, 2011) and Nilsagard et al. (Nilsagard, von Koch, Nilsson, & Forsberg, 2014).

An Error Rate is used to describe intensity of an exercise and thereby the level of the challenge (Fig. 2). The therapist adds and adjust tasks aiming at an adequate level of challenge, corresponding to an error rate of 20–40%. This means that an exercise executed at “moderate” intensity is conducted with approximately 60–80% error free repetitions, cycles or time depending on the task/exercise.

When supervising an exercise, an adequate level of challenge for a simple exercise is determined. After several successful executions of the exercise, cognitive and/or motor tasks are added when possible – in this study defined as “dual task”. Manipulation of sensory conditions by elimination of vision and performing exercises on a foam will also be applied. By adding motor or cognitive tasks, performance quality declines, but it should not exceed an error rate of 40%. In case of a higher error rate, the motor challenge is reduced, to lower the error rate.

Due to differences in patients’ level of function, symptoms, and training experience, the perceived challenges from the same exercise will differ between subjects. Hence, the BMCT framework has been developed in an attempt to standardize the training protocol in a way that allows the therapist to tailor and vary the exercises with respect to the patient’s individual functional level and needs, while ensuring that all patients receive exercises in the same domains and at a similar relative intensity.

3.2. Control group

The control group is on a waiting list during the first 10 weeks where they are encouraged to maintain usual care and level of physical activity. Hereafter they will receive an intervention with one weekly session of BMCT and one weekly session of PRT. Both sessions will start out with a 10-minute warm-up on a
stationary bicycle or treadmill. BMCT will be carried out in accordance with the described protocol for the BMCT-group. PRT consists of the same exercises as prescribed for the PRT-group but only an intensity of 12 RM is applied during the 10 weeks due to fewer sessions of PRT.

3.3. Adherence

All interventions are carried out in groups of 3–6 patients. To ensure adherence to the predefined protocol, physiotherapists will be instructed by the primary investigator on how to provide the interventions as well as receive written guidelines describing the exercises and the applied progression model. The therapists will register how training went in terms of type and execution of exercises, level of intensity and repetitions. The physiotherapist in charge of the intervention at the participating physiotherapy clinic registers symptoms of possible adverse events related to training. Any adverse event is then reported to the primary investigator who then reports to the Regional ethical committee.

3.4. Primary outcomes

Gait will be measured by the Timed 25 Foot Walk and the Six Spot Step Test. Gait function is a complex phenomenon where the interpretation highly dependent on what aspect of function is in focus – e.g. speed, coordination, duration, generation of force or task oriented gait. As the two interventions under investigation may have different effects on gait function (cf. the hypotheses), a design with two primary outcomes was chosen, that include a simple test of maximal gait speed (T25FW) and a test of more complex gait that include elements of balance and coordination (SSST). Perspectives on clinical relevant changes are published for T25FW (Baert et al., 2014) and SSST (H. B. Jensen, Mamoei, Ravnborg, Dalgas, & Stenager, 2016).

3.5. Timed 25 Foot Walk

Patients complete a T25FW (s) on a 10-meter walkway at fastest safe walking speed (FWS), respectively. Timed 25-Foot Walk (T25FW) has been validated in MS as one of the three components of the Multiple Sclerosis Functional Composite (MSFC) (Fischer, Rudick, Cutter, & Reingold, 1999). A limitation of the T25FW, is a floor effect seen in patients with mild disability (Kalkers et al., 2000). This is explained by the short walking distance, where the consequences of fatigue, spasticity, and inadequate coordination and balance will not manifest clearly (Nieuwenhuis, Van Tongeren, Sorensen, & Ravnborg, 2006; Schwid et al., 1999).

3.6. Six Spot Step Test

The SSST involves walking as fast as possible across a rectangular course, while kicking five blocks out of their circles marked on the ground. Compared to the T25FW, which reflects a certain degree of monotonous and automatized movement pattern, the SSST can be seen as a more complex task that requires an ongoing adaptation in terms of orientation, speed and limb support. As such, the SSST seems to be a better expression of complex lower-limb function than maximal straight-line walking.

SSST is superior to T25FW in discriminating ambulatory function across levels of disability (Nieuwenhuis et al., 2006), though it still calls for further validation and evaluation of psychometric properties such as responsiveness. Some perspectives on a clinical relevant change have been presented but more data is required.

3.7. Secondary outcomes

3.7.1. Fatigue

Fatigue is measured by the Danish version of the modified fatigue impact scale (MFIS). The MFIS is a multidimensional scale designed to assess the perceived impact of fatigue related to different aspects of daily life. It consists of 21 standardized questions where each item has five levels of response. The scale assesses perceived impact of fatigue on physical, cognitive and psychosocial function (Fisk et al., 1994). MFIS is reliable in people with MS (Learmonth et al., 2013).

3.7.2. Endurance and self-reported gait function

The six-minute walk test (6 MW) induces an endurance component and is therefore more prone to exhaust patients. The 6 MW has been shown to capture motor fatigue, as the test might affect gait pattern and reveal a change in motor strategies after rehabilitation (Leone et al., 2016). Outcome is the distance (m) walked per minute and total distance covered in 6 minutes. Additionally, the distance covered in the first and the sixth minute is registered (Leone et al., 2016). The 6 MW is a feasible, reproducible, and reliable mea-
sure (Goldman, Marrie, & Cohen, 2008). To measure the subjectively experienced impact of MS on walking ability, the 12-item MS Walking Scale (MSWS) (Hobart, Riazi, Lamping, Fitzpatrick, & Thompson, 2003) is used. The quality of the questionnaire evaluated from a graded response model is found to be good (Mokkink, Galindo-Garre, & Uitdehaag, 2016). The current validity of the scale in terms of psychometric properties is primarily based on correlations with measures of gait speed (T25FW) (Kurtzke, 1983) and distance (6 MW) (Goldman et al., 2008; Pilutti et al., 2013), despite these measures would expectedly only partly explain the MSWS score.

3.7.3. Temporospatial and kinetic measures

Walking at fastest and at self-selected speed is recorded by a Qualisys system including seven ProReflex infrared high-speed cameras. The subjects are equipped with 37 retro-reflexive markers mounted on the skin according to Visual 3D® marker set guidelines. The tests are performed bare-footed unless orthosis or other gait assistive devices prevent this. The system collects kinematic data for a three-dimensional analysis of gait function and is used for analysing: step and stride length, step width, time in swing and stance, gait speed and hip and knee angle during gait. A thin carpet on the walkway hides the force plate and patients strike the force plate with one foot. The test is repeated in order to measure foot strike on the opposite side. From the force plate data, a standard three-dimensional inverse-dynamics method is used to quantify the relevant forces and moments acting on the lower limb joints (Everett & Kell, 2010). Combined with angular joint velocity the peak net joint power, normalized to body mass (W/kg) can be calculated.

3.8. Balance

Static balance is measured using the “(modified) Clinical Test for Sensory Interaction and Balance (CTSIB)” (Shumway-Cook & Horak, 1986). The somatosensory, visual, vestibular systems and their interactions are essential for postural control and the test investigates the organization of sensory inputs for postural control.

The CTSIB test assesses the influence of sensory interaction on postural stability. This is done by compromising one or more senses during 30 sec stance in four conditions: 1) eyes open 2) eyes closed 3) eyes open standing on foam 4) eyes closed standing on foam. CTSIB is performed at a force plate to register displacement of COM. Outcome is trajectory path length and ellipse area (Kalron, Nitzani, & Achiron, 2016).

Mini-BESTest is a 14 item function test that measures dynamic balance (Franchignoni, Horak, Godi, Nardone, & Giordano, 2010). The mini BESTest is a reliable measure of balance and it has shown good discriminatory properties for identifying abnormal postural response (King, Priest, Salarian, Pierce, & Horak, 2012) as well as for determining the risk of fall in patients with Parkinson’s (Ross et al., 2016). The “Activities-specific Balance Confidence Scale” (ABC) questionnaire assesses balance confidence in 16 different activities from everyday life (Powell & Myers, 1995) that requires static, dynamic, proactive and reactive balance. It was developed as an instrument to detect risk of falling in elderly people, but has also been used for persons with MS. It is validated using an Italian translation (Cattaneo, Regola, & Meotti, 2006). It is believed that confidence in the bodily abilities is a prerequisite for bodily actions. Hence, in this study the correlation between objective and subjective balance-measures is determined.

3.9. Strength

3.9.1. Maximum isometric and isokinetic muscle strength

Maximum voluntary contraction (MVC) of the knee flexors (KF), knee extensors (KE), dorsal flexors (DF) and plantar flexors (PF) are determined by a Cybex Norm dynamometer (Humac Norm, CSMi, Stoughton, MA, USA). The individual settings of the dynamometer are registered and used during the retest. Isometric muscle strength in KE and KF is tested at 70 and 30 degrees flexion, respectively. Isometric PF and DF are tested with the knee extended and the ankle in 0° and 25° flexion, respectively and isokinetic (60°/sec.) strength is tested in a range of motion going from 10° dorsal flexion to 25° plantar flexion.

The patients maximally extend their knee for approximately 4 seconds followed by a 30 sec. rest. This sequence is repeated 3 times. The torque signal is sampled at 100 Hz, and peak torque is determined as the highest attained torque during a single attempt.

3.10. Health related quality of life

Information on health status is measured by the Short-Form Health Survey (SF-12) (Jenkinson et al., 1997; Ware, Kosinski, & Keller, 1996). It is a generic
questionnaire evaluating physical and mental health that was developed to provide a shorter alternative to the SF-36. Scores on both physical and mental health is found reliable and valid (Cheak-Zamora, Wyrwich, & McBride, 2009). The questionnaire is generic and does not specifically target issues related to MS.

3.11. Sample size

Sample size is estimated from an expected change in gait speed assessed by Timed 25 foot walk (T25FW) and the Six Spot Step Test (SSST). The effect of each intervention are compared to the control group (effect = 0, Power = 0.80 and level of significance = 0.05). As two primary outcomes (T25FW and SSST) are applied the sample size estimation is based on four different calculations (two for each intervention):

1. **PRT evaluated by T25FW**: A study evaluating a comparable PRT intervention found a 12% increase in gait speed (Dalgas et al., 2009) with an SD of 8%. With a similar result 7 participants in each group are required.

2. **PRT evaluated by SSST**: In an unpublished study, a group of comparable patients conducted 30 weeks of PRT (H. Jensen et al., 2015), showing an increase of 16.8%, SD = 15%. From this estimate, 13 participants in each group are needed.

3. **BMCT evaluated by T25FW**: Studies on elderly with osteoporosis (Halvarsson, Franzen, & Stahle, 2015) are used as no relevant studies in MS could be located. Twelve weeks of balance training resulted in an 8% increase in gait speed, SD = 11% (data from Halvorsson et al. (Halvarsson et al., 2015) and personal communication). Based on this estimate 29 participants are required in each group.

4. **BMCT evaluated by SSST**: No publications usable for the power calculation were found.

In summary, 32 patients in each group (total n = 96) will be sufficient, when assuming a dropout rate of 10%.

3.12. Statistical analysis

The effects observed from baseline to follow-up on T25FW, SSST and secondary outcomes in the three groups is examined in a mixed effects regression analysis with group and time as fixed effects and center and patient within center as random effects. This takes into account that observations on different patients at the same center are typically better correlated than what is seen in patients from different centers. Similarly, the stronger correlation among observations on the same patient compared to different patients at the same center is accounted for.

It will be checked whether the assumption of equal variance and a normal distribution of residuals is met based on the mixed effect model. In case of violation of assumptions the analyses will be carried out on a logarithmic scale.

Descriptive statistics will be used to present and compare characteristics across groups at baseline and to determine the distributional properties of the data. Spearman or Pearson correlation analysis will be conducted on baseline data from all patients that underwent baseline testing in order to determine associations between the primary outcomes and the secondary outcomes on fatigue, spatial gait parameters, balance and self-reported measures.

Analyses will be carried out as intention-to-treat where all patients that are tested at follow-up are include regardless of their compliance to the protocol. In case of low adherence, a supplementary per-protocol analysis will be performed, where attendance according to the protocol will be defined as participants having a minimum of 80% attendance (corresponding to 16 sessions out of 20). Level of significance is set at 0.05.

4. Discussion

This RCT will expand our understanding of how different rehabilitation interventions affect gait, balance and fatigue and the study will thereby help optimizing future rehabilitation interventions in persons with MS. Moreover, not many studies evaluate different related rehabilitation interventions in a head to head design in persons with MS. Expectedly, BMCT will improve balance (Gandolfi et al., 2015; Paltamaa et al., 2012), while PRT will improve muscle strength (Kjolhede et al., 2012). However, neither the size of the effects, nor whether one intervention is superior to the other is clear, when evaluated by a functional test relying on both strength and balance.

The amount of high quality literature on PRT is substantially larger (Kjolhede et al., 2012) than on BMCT (Paltamaa et al., 2012). This may in part, be explained by the scientific feasibility of PRT in terms of standardization, where intensity and exercises
are easily defined and described and where muscle strength outcomes can be highly standardised and easily determined. Despite the extensive use in physiotherapy practise, BMCT is harder to fit into a highly standardized protocol, as required when causation is investigated. Moreover, improvement of balance and motor skills that are transferable to everyday tasks require BMCT that is tailored with respect to repetition and variation in the applied exercises (Carr & Shepherd, 2010). Despite the challenges when investigating BMCT it may pose elements that are complementary to PRT, and addition of BMCT may therefore help optimize motor rehabilitation in MS.

Execution of gait is the result of a complex interaction between the environment, physical and cognitive abilities and the task (Shumway-Cook & Woollacott, 2017). Hence, manipulation of either sensory input, cognitive requirements or task-oriented demands affects motor processing and can potentially alter movement pattern during gait. In order to provide an exercise intervention that transfers into improved functional ability during complex use in everyday life, variation in exposure during exercise is advised (Nielsen et al., 2015). To address this issue, the framework developed for the BMCT intervention defines training in stations that ensures variation. Moreover, the BMCT exercises at a given station are altered and adjusted, as the program progresses, but the functional aim and duration at a given exercise station is maintained.

This concept of tailored exercises that varies across patients, calls for a discussion of the reproducibility of particularly the BMCT intervention. In this study, the idea is to standardize the treatment paradigm rather than the treatment itself. The therapists are provided reliable rules for the content and progression, but without specifying the exercises. Intensity of BMCT is then determined from the level of difficulty (the error rate) interpreted from the quality of the execution of a particular exercise. When performing BMCT, the level of function is to a greater extent dependent on cognitive processing than during PRT. This is primarily explained by increased requirements in relation to fine motor function, divided attention and the continuous exposure to new tasks. All though, muscle strength is still related to performance.

Regarding standardization, two patients with different clinical characteristics will receive different BMCT interventions, while subjects with similar characteristics will receive a comparable intervention. Despite diverse BMCT exposure, the participants are similarly challenged relative to their motor control ability. Likewise in the PRT intervention, loads differs across patients depending on their strength level.

For the BMCT, therapists select and adjust exercises aiming at an error rate of approx. 20–40%. It can be argued, that the dependency of the physiotherapeutic skill combined with the multi-center design, where interventions are carried out by different therapists, will pose a threat to the validity of the study. On the contrary, it can be argued that a BMCT intervention, with only one therapist in charge of all training sessions, tend to reflect only one person’s handling of the prescribed intervention. In the present study, the external validity is thought to be high since the treatment is performed in a real clinical setting, is provided by therapists experienced in MS rehabilitation, is implemented into the framework of the national health care system and that the inclusion and exclusion criteria are quite wide.

The SSST and the T25FW are the primary outcomes that evaluate function capacity. However, from the array of secondary measurements it will be possible gain insight into a potential diverse effect of PRT and BMCT when looking in muscle strength and balance, fatigue, gait characteristics and the self-reported level of function. Additionally, as the effects are results of rehabilitation conducted at different clinics, data allows for stratification, to determine systematically differences across the participating centers that provide the same intervention. This might give rise to future studies of the management of guidelines in clinical practice.

Authors’ contributions

JC contributed to the conception and design of the study and drafted the manuscript. UD contributed to the conception and design of the study and edited the manuscript. DC contributed to the conception and design of the study and edited the manuscript. JB contributed to the conception and design of the study and edited the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

JC, DC and JB declare that they have no conflict of interests associated with this paper. UD has received research support, travel grants and/or teaching hon-
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