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Translational approaches in neurorehabilitation: from Researcher's bench to Patient's bedside

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Introduction

Exercise physiology studies the acute and chronic responses of biological systems to exercise. It provides sports and medical practitioners with updated evidence-based tools to optimize and fine-tune the training process in order to obtain the highest and most appropriate adaptations to a wide range of exercise conditions. Scientific reports on this topic provide guidance on the proper assessment of motor functions as well as on the best methodologies to improve them through training regimens. While such approach is conventionally employed when the athlete's performance is scheduled for analysis and enhancement, this is not the case of individuals presenting with neurological conditions whose functional impairments and consequent disability are generally addressed through quite elementary training approaches. In the consideration of such discrepancy, the endeavor of the present work was to verify the feasibility of translating evidence-based methodologies and techniques from exercise and sports physiology to the neurological environment.

Is this approach feasible?

Is it appropriate?

Is it dangerous?

Is it *effective*?

To answer these question we started focusing on muscle strength since muscle weakness is among the most frequently reported disabilities induced by neurological disorders and dramatically affects the activities of daily living and, consequently, the quality of life of this category of patients.

Therefore, the project of the author's PhD had as its primary objective the functional assessment and treatment of patients with diseases of the nervous system through the employment of methodologies developed and used in sports and exercise physiology research and their translation in the rehabilitation of neurological disorders. In this perspective, the main focus of this doctoral program was the appraisal of muscle strength in its biomechanical and functional components, first in populations of healthy subjects and immediately after in populations of individuals with neurological conditions, with a specific emphasis on multiple sclerosis. The rationale behind the project was that neurological patients do not fully benefit from the opportunities offered by functional assessment techniques that are crucial for the optimal quantification of disability but also of the best training methodologies which are essential to structure evidence-based and effective neurorehabilitation paths.

In the author's intention, the present PhD project report is meant to be viewed as a 7-stage journey, with seven published papers on muscle strength stepping from the healthy paradigm into the neurological patient's bedside.

Study 1. Isokinetic testing of muscle performance: new concepts for strength assessment.

1.1 ABSTRACT

Background: Peak torque (PT) is considered the most representative parameter of muscle performance in isokinetic dynamometry while other computable parameters such as mean peak torque (MPT), maximal work (maxW) and mean work (meanW) are generally neglected.

Objectives: This cross-sectional study reassessed whether PT is the only necessary parameter in isokinetic testing and weighed the contribution of each variable to muscle performance.

Methods: Thirty apparently healthy volunteers underwent unilateral isokinetic assessment of the ankle dorsiflexion of both legs at 45 and 90°/s. Bivariate relationships and multivariate associations between PT, MPT, maxW and meanW were examined employing Pearson's analysis and principal component analysis (PCA), respectively.

Results: At both velocities, Pearson's coefficients were very high between PT and MPT as well as between maxW and meanW ($r>0.9$; $p<0.0001$) and fair-to-good ($r=0.65$-0.73; $p<0.0001$) between torque and work measures. At 90°/s the PT and MPT mostly contributed to muscle performance while at 45°/s, MPT and meanW exhibited the highest component loadings, whereas PT performed poorly.

Conclusions: Isokinetic variables contributed with different loadings to muscle performance of ankle dorsiflexors, depending on the angular velocity employed. In particular, work measures may usefully complement the conventional PT-only analysis, especially in rehabilitative settings where low speeds are recommended.

1.2 INTRODUCTION

Strength assessment allows accurate quantification of training or treatment efficacy as it provides baseline and post-intervention data [1]. Isokinetic dynamometry is considered the "gold standard" in the assessment of muscle strength with modern devices supplying trainers and clinicians with a plethora of parameters [2]. Among these, the peak torque (PT) is conventionally considered the most consistent and reliable as well as the most commonly reported index in isokinetic tests [2, 3]. Although incorporated in testing reports other parameters such as the mean peak torque (MPT), work and power, are generally neglected [2, 4]. Several studies have analyzed the relationship between PT and the other strength parameters in lower limb muscle groups, including ankle plantar flexors and dorsiflexors [4] as well knee flexors and extensors in both physiological [5] and pathological conditions [7, 8]. In these reports, the finding of a moderate to high Pearson's r correlation coefficient (in excess of 0.7) of PT with MPT, work and power, has led to the general belief that PT may be the only necessary parameter for isokinetic muscle performance testing [7]. Conversely, Kramer and MacDermid [8] stated that these measures were not identical and, in agreement with them, Dvir and David [9] specified that a high linear correlation *per se* does not necessarily render the interchangeable use of these parameters legitimate.

PT is defined as the highest muscular moment output along the tested range of motion and stands for the muscle's maximum strength capability [3]. MPT represents, instead, the average moment based on a set of maximal repetitions. While PT and MPT are expected to be highly related, the relationships of PT with power and work deserve separate mentions.

Some devices measure the instantaneous peak power, while most of the available machines only report the average power. Since average power is calculated dividing the amount of work of a movement by the time required to accomplish it, its use in the interpretation of isokinetic data may raise collinearity concerns.

Regarding work, the average of the 'works' recorded over a set of repetitions is also known as the mean work (meanW); it h has been associated with endurance/fatigue analysis where the meanW of the last 3-5 repetitions is compared to the meanW of the initial 3-5 repetitions. However, the meanW is seldom if ever considered in isokinetic strength assessment. Maximal work (maxW) is the total muscular force output for the repetition with the greatest amount of work. A specific debate has been raised whether it should be reported along with PT or neglected since they have been shown to be equivalent, rendering the necessity of each measurement questionable [2, 4, 7]. Although PT and maxW are simultaneously recorded from the same repetition/joint movement, they provide quite different information: PT represents the single highest point of the curve whereas maxW is the total area under the best torque curve [5]. While PT is an instantaneous measure of strength exerted at one single point, maxW is the average measure of the torque output throughout the entire range of motion [6]. Morrissey suggested that performing only a PT-based analysis may lead to overestimation of the muscular torque output throughout the remaining range of motion [6]. For these reasons, maxW is considered a better indicator of muscle function than PT, particularly in rehabilitative settings [3, 9]. Although several reports have addressed this topic, to date and to our knowledge the relationships between PT, MPT, maxW and meanW have been investigated exclusively in terms of Pearson's correlation coefficients.

The present study proposes, therefore, to reassess the conventional position whereby PT may be the only necessary parameter in isokinetic strength testing and to weigh the contribution of each variable to muscle performance. Such aim was pursued: *i)* using the ankle dorsiflexion muscles in view of their unique role in human locomotion functioning and of the clinical implications of their impairment [10]; *ii)* employing isokinetic dynamometry whose validity and reliability was verified by calculation of intraclass correlation coefficient (ICC); *iii)* employing the principal component analysis (PCA), which is a multivariate technique well-suited to find the most informative or explanatory data features, without needing an *a priori* knowledge [11]. This statistical approach converts a set of possibly correlated variables into a smaller set of values of linearly uncorrelated variables, called principal components, which retain most of the variation present in the original data set.

1.3 METHODS

1.3.1 Participants

Thirty healthy untrained subjects were selected among university students and staff (21 males, 9 females; 26.7±4.6 years old; 70.5±12.0 kg) and deemed eligible to be enrolled in the present cross-sectional study. Participation in any sporting activity on a regular basis, even recreational, was set as a criterion for exclusion. All subjects signed an informed consent before enrollment. The study (ClinicalTrials.gov identifier: NCT02010398) was conducted in accordance with the Declaration of Helsinki and approved by the local Bioethics Committee of ASL n.1-Sassari, Italy (ID: Prot. 1160/L). All testing procedures were performed at a consistent time of the day and by the same operator. No verbal encouragements were provided during data collection, to avoid any bias deriving from the operator-subject interaction [12]. Data were collected in the laboratory of Human Physiology and Applied Neurophysiology of the Department of Biomedical Sciences, University of Sassari, from September 2013 to May 2014.

1.3.2 Muscle Performance Testing

Muscle performance of the ankle dorsiflexors (DF) was assessed using an isokinetic dynamometer (Biodex System 3 PRO, Biodex Medical Systems, Shirley, NY, USA). In a separate session, participants were allowed to become familiar with the dynamometer and with the proposed motor task consisting of isolated submaximal dorsiflexion of the ankle joint. Such procedure was employed to minimize the potential effects of learning associated to strength-testing procedures [13]. The apparatus was calibrated and assembled with the ankle attachment according to the manufacturer's specifications; gravity compensation analysis was performed by the software provided with the machine [14]. The dynamometer shaft was aligned with the assumed axis of rotation of the ankle (lateral malleolus). The subject was positioned with the knee flexed at 30° and the ankle in full plantar flexion taken as starting point. The position of the ankle was firmly secured to the dynamometer with supplied straps. Extraneous body movements were minimized by restraining each subject with shoulder harnesses, hip belts, mid-thigh and ankle restraint straps. During the tests subjects were not allowed to grasp the bench handles. Arms were placed across the chest with hands holding on to the straps [15]. Before testing, participants underwent a predefined 5-minute warm up practise by performing one set of 6-8 submaximal repetitions at 45 and 90°/s, with a 2-3-minute rest in between. After a 5-minute rest, the following primary outcome parameters were recorded at both angular velocities: PT, MPT, maxW, meanW and average power.

A retest procedure was performed within one week from the initial assessment, to estimate the reliability and consistency of the measurements. To this aim the intra-class correlation coefficients were calculated taking an ICC value <0.4 as an index of poor reliability, 0.4 to 0.75 fair to good reliability, and >0.75 excellent reliability [16].

1.3.3 Data analysis

Statistical analyses were performed using STATA 12 (StataCorp, College Station, Texas). Validity and reliability of measurements provided by the Biodex System 3 PRO were assessed employing a two-way random single measures intra-class correlation coefficient ($ICC_{2,1}$) according to Shrout and Fleiss [16]. Sixty measures obtained from the two limbs of thirty subjects were analyzed and considered together for statistical analysis since the variability of the distributions of the two limbs, previously calculated by the coefficient of variation, was not different between sides. Descriptive analyses were carried out for variables studied at each angular velocity. The Shapiro-Wilk test was used to assess normality of the variables. Since this assumption was met for all variables, the parametric Student's *t* test was employed to evaluate the difference between the average measurements of muscle performance variables at both velocities. Prior to the multivariate approach, a preliminary regression analysis was performed to explore the appropriateness of the model [17]. This exploratory analysis revealed collinearity between average power and maximal work leading to discarding power from the subsequent analyses.

1.3.4 Correlation analysis

Pearson's correlation analysis was used for bivariate correlation between PT, MPT, maxW and meanW at the two velocities.

1.3.5 Principal component analysis (PCA)

Principal component analysis was performed as a multivariate correlation approach aimed at finding the eigenvectors (factors) and eigenvalues, which indicate the amount of variance accounted for each component.

Kaiser-Meyer-Olkin measure of sampling adequacy was found to be meritorious (KMO index = 0.84) [18]. A scree plot of the eigenvalues associated with each factor was employed to determine the number of factors to retain: only those factors whose eigenvalues were greater than 1 were retained, according to the Kaiser method [19]. A variable was clearly considered to load on a factor if the loading on the factor was >0.5.

1.4 RESULTS

No drop-outs occurred in this study so data obtained from the 30 subjects screened and enrolled were analyzed. Descriptive statistics and the results of reliability analyses are both reported in Table1.

Mean values of performance at 45°/s were significantly higher than those recorded at 90°/s for all variables (p <0.0001). Concerning reliability, ICC coefficients were higher than 0.9 at both angular velocities.

The correlation matrix of Pearson's coefficients is reported in Table 2 at 90°/s and 45°/s. Statistically significant correlations between all muscle performance variables (PT, MPT, maxW and meanW) were observed at both angular velocities (p<0.0001). MPT and PT showed the highest correlation coefficients (Pearson's r=0.96-0.97; p<0.0001). At both angular velocities, a fair-to-good Pearson's correlation coefficient (Pearson's r=0.65-0.73; p<0.0001) was found between torques (PT and MPT) and work measures (maxW and meanW).

Regarding PCA, only the first principal component of the total variance showed an eigenvalue >1 and was therefore extracted. The component extracted accounted for the largest amount of total variance in percentage (81% and 83% at 90°/s and 45°/s, respectively). The loading factors onto the first principal component are detectable by the one-dimensional representation in Figure 1. At 90°/s of angular velocity, the weights of the variables onto the component 1 were different, with torques (PT and MPT) and work measures (maxW and meanW) being organized in two clusters. Only PT and MPT showed loadings >0.50 (0.52 and 0.51, respectively). A different scenario was observed at 45°/s: all variables, in fact, are likely to contribute to muscle performance but, in this condition, only MPT and meanW showed a loading factor >0.50 (0.51 and 0.507, respectively).

1.5 DISCUSSION

The present study investigated in depth the relationships between PT, MPT, maxW and meanW and identified the parameters best describing muscle performance of the ankle DF. The classic linear correlation approach showed that these variables were highly associated, suggesting that they are equivalent in describing muscle performance. However, principal component analysis interestingly indicated that PT, MPT, maxW and meanW contributed with different weights to muscle performance, depending on the testing condition.

1.5.1 Linear correlation analysis

Trial-to-trial reliability of measurements of the isokinetic Biodex System 3 PRO used in this study proved excellent (ICC= 0.93-0.98), both at 90°/s and 45°/s of angular velocity, confirming that this is a reliable and valid instrument for collection of dynamometric data [20, 21].

According to previous reports [2, 4, 6, 7] our study has yielded moderate to very high Pearson's correlation coefficients between PT, MPT, maxW and meanW. This finding was expected since measurements were performed during the same muscle movement (PT and maxW) or the same repetition set (MPT and meanW). An acknowledged criterion for establishing interchangeability between different measurements is a correlation coefficient of at least 0.80 [22]. Consistently with data from knee extensors and flexors [6, 7] , the Pearson's r >0.9 between PT and MPT we found in ankle DF suggests that these variables may be interchangeable, with one of the two finely representing the other, so that only one is strictly necessary, also when testing performance of this muscle group. The same applies to the relationship between maxW and meanW. As for the relationships between torque and work measures, the correlation coefficient we observed in the ankle DF was 0.6-0.7, in line with previous observations in the same muscle group [7]. In the light of the abovementioned criterion [22], interchangeability may not apply to these variables. Higher coefficients between PT and work were found in the knee flexors and extensors, which led to the conclusion that these variables are interchangeable [6, 23]. Discrepancies in the correlation coefficients reported in the literature raise issues on the role played by each variable contributing to muscle performance, which seems different depending on the muscle group [9]. As far as we know, no studies have examined yet the relationship between the anatomo-functional features of different muscle groups acting at different joints and the patterns of contribution to muscle performance in terms of PT, MPT, maxW and meanW.

Since Pearson's coefficients between the variables were also quite similar at the two different angular velocities (90 and 45°/s), it seemed that linear correlation was unresponsive to changes in the testing condition. Such changes were instead revealed by the PCA approach, which better weighs the components of the total variance explained by each variable [24], thus defining the hierarchy of contributions to muscle performance more accurately than linear correlation analysis alone.

1.5.2 Principal Component Analysis

PCA, unlike linear correlation, proved to be quite sensitive in ranking the variables' contributions to muscle performance depending on the angular velocity employed, which is a crucial concept in isokinetic testing and training. PCA works best when collinearity among variables is excluded [17] and when the variables in the original dataset are highly correlated [25]. In this case, fewer components are required to capture common information [26]. For these reasons, PCA was well-suited to our muscle performance variables which were highly correlated and with only one principal component extracted for analysis. This does not apply to average power which was found to be collinear with maximal work and, therefore, inappropriate for the PCA model.

At 90°/s the PT showed the highest loading factor on muscle performance being, therefore, the parameter best explaining its variability. This is consistent with previous reports that acknowledged PT as the most consistent and reliable parameter in isokinetic testing [2, 4]. However, this pattern was not confirmed at the testing condition of 45°/s, where MPT was the variable showing the highest loading factor, followed by meanW. In this testing condition, meanW and maxW performed better than PT, showing higher loading factors. This finding is in disagreement with previous works that, based on moderate to high correlation coefficients between the above considered variables, conventionally support PT-based analysis alone, acknowledging PT as well-representative of any other variable and possibly the only necessary parameter for isokinetic muscle performance testing [2, 4, 6, 7]. This opinion was questioned by other authors [8, 9], who stated that high linear correlations did not necessarily enable the interchangeable use of variables and concluded that muscle performance may be better represented by average than peak moments, depending on the muscle group and on the level of exertion [9]. In agreement with these reports our PCA-based data suggest that the considered variables contribute to muscle performance of ankle dorsiflexion muscles with a different weight, depending on the angular velocity. In particular, PT and MPT are likely to play a major role at intermediate velocities, which require a lower muscle effort, while MPT and meanW appear mainly involved at lower speeds requiring a higher level of exertion.

In this context, work analysis may offer valuable additional information to that attained by the conventional PT analysis, especially when low speed muscle contractions are employed, such as in the rehabilitation of neurological disorders [27, 28] and early phases of orthopaedic conditions [5].

However, extending these findings to muscle groups other than ankle DF could be inappropriate, since these muscles, particularly the tibialis anterior, are considered atypical from both the physiological and biomechanical points of view [29]. In this regard, it is worth mentioning that the tibialis anterior has a unique role in human locomotion during early stance phase, for preventing high-velocity plantarflexion, and during swing phase to ensure precision when the toe clears the floor [10, 29].

When choosing the variables best describing muscle performance, factors other than muscle group, angular velocity or level of exertion should be taken into proper account. For instance, work depends on the joint range of motion while PT is largely independent and, therefore, more reliable [30, 31, 32], whereas work and PT could be equally effective in endurance/fatigue analysis [33].

1.6 CONCLUSIONS

Despite the limited sample size that will need independent validation with further studies also in other muscle groups, the PCA findings, firstly reported in this study, may prove useful in choosing the most informative parameters of muscle performance in isokinetic strength testing and when assessing the efficacy of rehabilitative interventions. The analysis of not only the PT but also mean torques and work measures, depending on the velocity of contraction employed, may prove of interest both in sports science scenarios as well as in rehabilitation settings. Particularly, in the assessment of ankle DF, the critical role of PT as the gold standard in isokinetic analysis is well maintained at intermediate angular velocities, while, at lower angular velocities, work measures can complement the PT in providing a more comprehensive picture of muscle performance.

1.7 Table And Figure

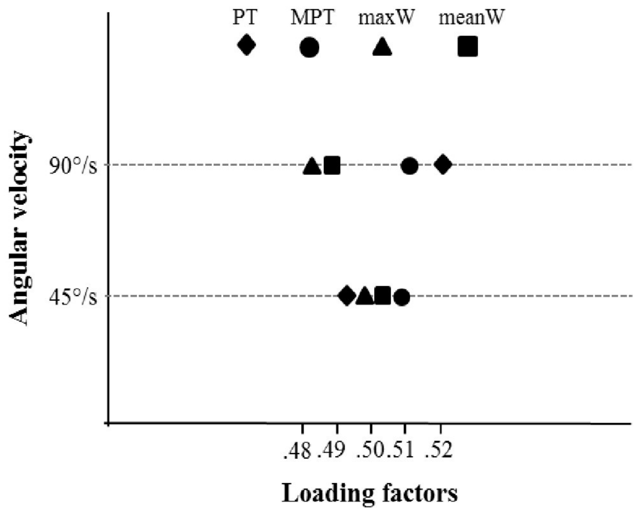


Figure 1. Loading plot of muscle performance variables using one-dimensional projections onto the first principal component, at 90 and 45°/s. PT = peak torque; MPT = mean peak torque; maxW = maximal work; meanW = mean work.

Table 1 - Descriptive statistics and intra-machine reliability of ankle dorsiflexion muscle performance as tested by the Biodex System 3 PRO at 90 and 45°/s.

Angular Velocity		Peak torque (Nm)	Mean torque (Nm)	Maximal work (J)	Mean work (J)
90°/s	Test value	37.5 ± 9	32.9 ± 7.5	16.5 ± 5.1	12.9 ± 4.5
	Retest value	39.4 ± 9.2	34.7 ± 8.3	18.1 ± 5.4	14.3 ± 5.2
	$ICC_{2,1}$	0.95	0.96	0.93	0.94
	ICC 95% C.I.	0.92 – 0.97	0.94 – 0.98	0.89 – 0.96	0.91 – 0.96
45°/s	Test value	44.3 ± 11	40.6 ± 10.1	19.4 ± 7.7	18.2 ± 7.4
	Retest value	46.7 ± 12.2	43.1 ± 11.8	21.6 ± 8	18.7 ± 9.3
	$ICC_{2,1}$	0.98	0.96	0.96	0.97
	ICC 95% C.I.	0.97 – 0.99	0.94 – 0.98	0.95 – 0.98	0.95 – 0.98

Nm =Newton*meter; J =joules; °/s = degrees/second of isokinetic angular velocity; test =assessment performed at baseline; retest = re-assessment within one week from baseline; test and retest values are reported as mean ± SD; $ICC_{2,1}$ = intra-class correlations; 95% C.I.= Confidence Interval at 95%.

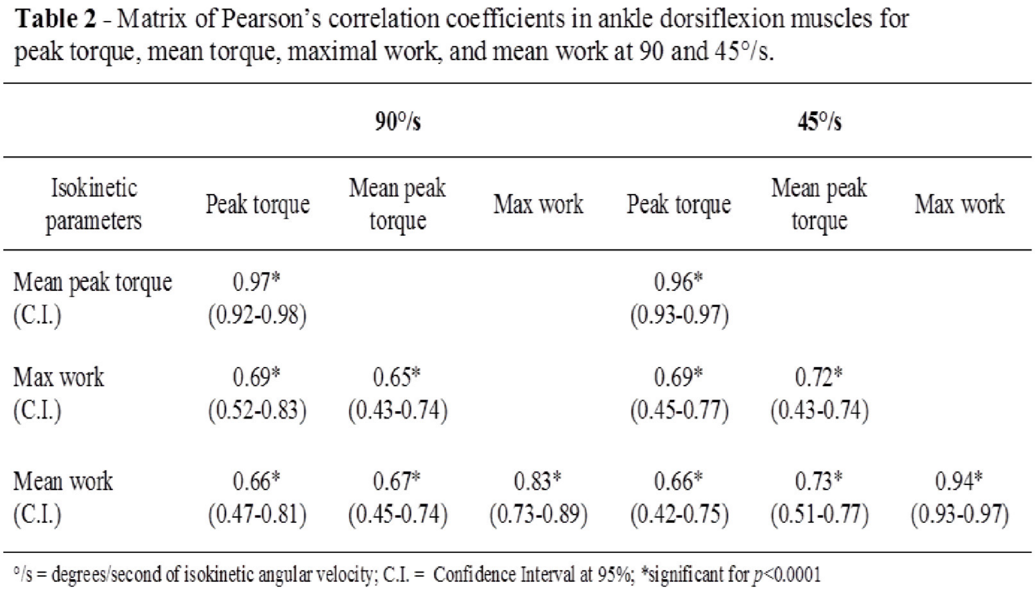


Table 2 - Matrix of Pearson's correlation coefficients in ankle dorsiflexion muscles for peak torque, mean torque, maximal work, and mean work at 90 and 45°/s.

	90°/s			**45°/s**		
Isokinetic parameters	Peak torque	Mean peak torque	Max work	Peak torque	Mean peak torque	Max work
Mean peak torque (C.I.)	0.97* (0.92-0.98)			0.96* (0.93-0.97)		
Max work (C.I.)	0.69* (0.52-0.83)	0.65* (0.43-0.74)		0.69* (0.45-0.77)	0.72* (0.43-0.74)	
Mean work (C.I.)	0.66* (0.47-0.81)	0.67* (0.45-0.74)	0.83* (0.73-0.89)	0.66* (0.42-0.75)	0.73* (0.51-0.77)	0.94* (0.93-0.97)

°/s = degrees/second of isokinetic angular velocity; C.I. = Confidence Interval at 95%; *significant for $p<0.0001$

1.8 REFERENCES

1. Stark T, Walker B, Phillips JK, Fejer R, Beck R. Hand-held dynamometry correlation with the gold standard isokinetic dynamometry: A systematic review. PM&R. 2011; 3(5):472-479.
2. Kannus P. Isokinetic evaluation of muscular performance: Implications for muscle testing and rehabilitation. Int J Sports Med. 1994; 15(1):11-18.
3. Davies, GJ. A Compendium of Isokinetics in Clinical Usage and Rehabilitation Techniques. 4th ed. Onalaska, WI. S. & S Publishers; 1992.
4. Woodson C, Bandy WD, Curis D, Baldwin D. Relationship of isokinetic peak torque with work and power for ankle plantar flexion and dorsiflexion. J Orthop Sports Phys Ther. 1995; 22(3):113-115.
5. Perrin DH, Robertson RJ, Ray RL. Bilateral isokinetic peak torque, torque acceleration energy, power, and work relationships in athletes and nonathletes. J Orthop Sports Phys Ther. 1987; 9(5):184-189.
6. Morrissey MC. The relationship between peak torque and work of the quadriceps and hamstrings after meniscectomy. J Orthop Sports Phys Ther. 1987; 8(8):405-408.
7. Bandy WD, Timm KE. Relationship between peak torque, work, and power for knee flexion and extension in clients with grade I medial compartment sprains of the knee. J Orthop Sports Phys Ther. 1992; 16(6):288-292.
8. Kramer JF, MacDermid J. Isokinetic measures during concentric-eccentric cycles of the knee extensors. Aust J Physiother. 1989; 35(1):9-14.
9. Dvir Z, David G. Average or peak moment: Which of the two is more suitable to represent isokinetic muscle strength? Isokinet Exerc Sci. 1995; 5(2):93-97.
10. Petersen NT, Pyndt HS, Nielsen JB. Investigating human motor control by transcranial magnetic stimulation. Exp Brain Res. 2003; 152(1):1-16.
11. Jolliffe IT. Choosing a Subset of Principal Components or Variables. In: Jolliffe IT, Principal Component Analysis. 2nd ed. Springer, 2009.

12. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev. 2001; 81(4):1725-1789.
13. Carroll TJ, Herbert RD, Munn J, Lee M, Gandevia SC. Contralateral effects of unilateral strength training: Evidence and possible mechanisms. J Appl Physiol. 2006; 101(5):1514-1522.
14. Biodex, Biodex System 3 Pro Manual (#835-000) Applications/Operations. Biodex Medical Systems, Inc, Shirley, NY; 1988.
15. Stumbo TA, Merriam S, Nies K, Smith A, Spurgeon D, Weir JP. The effect of hand-grip stabilization on isokinetic torque at the knee. J Strength Cond Res. 2001; 15(3):372-377.
16. Shrout PE, Fleiss JL. Intraclass correlation: uses in assessing rater reliability. Psychol Bull. 1979; 86(2): 430-428
17. Johnson RA, Wichern DW. Applied Multivariate Statistical Analysis. 6th Ed. Pearson, 2007.
18. Kaiser HF. A second generation Little Jiffy. Psychometrika. 1970; 35, 401-416.
19. Kaiser HF. The application of electronic computers to factor analysis. Educ Psychol Meas. 1960; 20: 141-151
20. Drouin JM, Valovich-McLeod TC, Shultz SJ, Gansneder BM, Perrin DH. Reliability and validity of the biodex system 3 pro isokinetic dynamometer velocity, torque and position measurements. Eur J Appl Physiol. 2004; 91(1):22-29.
21. Örtqvist M, Gutierrez-Farewik EM, Farewik M, Jansson A, Bartonek Å, Broström E. Reliability of a new instrument for measuring plantarflexor muscle strength. Arch Phys Med Rehab. 2007; 88(9):1164-1170.
22. Burdett RG, Van Swearingen J. Reliability of isokinetic muscle endurance tests. J Orthop Sports Phys Ther. 1987; 8(10):484-488.
23. Kannus VP, Latvala K. Torque acceleration energy, power and peak torque in thigh muscles after a previous knee sprain. Can J Appl Sport Sci. 1989; 14(2):103-106.
24. Jolliffe IT. Choosing a Subset of Principal Components or Variables. In: Principal Component Analysis. 2nd Ed. Springer, 2009.

25. Delis I, Berret B, Pozzo T, Panzeri S. A methodology for assessing the effect of correlations among muscle synergy activations on task-discriminating information. Front Comput Neurosci. 2013; 13: 7:54.
26. Manly BFJ. The material of multivariate analysis. In: Manly BFJ, Multivariate statistical methods: a primer, 3rd ed., Chapman & Hall/CRC, 2005.
27. Griffin JW, McClure MH, Bertorini TE. Sequential isokinetic and manual muscle testing in patients with neuromuscular disease. A pilot study. Phys Ther. 1986; 66(1):32-35.
28. El Mhandi L, Bethoux F. Isokinetic testing in patients with neuromuscular diseases: A focused review. Am J Phys Med Rehabil. 2013; 92(2):163-178.
29. Tallent J, Goodall S, Hortobágyi T, St Clair Gibson A, Howatson G. Corticospinal responses of resistance-trained and un-trained males during dynamic muscle contractions. J Electromyogr Kinesiol. 2013; 23(5):1075-81.
30. Reichard LB, Croisier JL, Katz-Leurer M, Malnati M, Dvir Z. Testing knee extension and flexion strength at different ranges of motion: an isokinetic and electromyographic study. Eur J Appl Physiol. 2005; 95:371-376.
31. Croisier JL, Malnati M, Reichard LB, Peretz C, Dvir Z. Knee extension and flexion strength and electromyographic activity at different ranges of motion: a reproducibility study. J Electromyogr Kinesiol. 2007; 17:484-492.
32. Reichard B, Katz-Leurer M, Rubinstein M, Croisier JL, Dvir Z. Short range of motion isokinetic testing of wrist flexors and extensors strength in normal subjects and patients with carpal tunnel syndrome. J Strength Cond Res. 2010; 24:1866-1873.
33. Porter MM, Holmbäck AM, Lexell J. Reliability of concentric ankle dorsiflexion fatigue testing. Can J Appl Physiol. 2002; 27(2):116-127.

Study2 : Characterization of ankle dorsiflexors performance in healthy subjects following maximal-intensity isokinetic resistance training

2.1 Abstract

The objectives of this study were: to bilaterally characterize the performance of ankle dorsiflexion muscles (DF) in terms of peak moment (PM), mean PM (MPM), maximal work and mean work (meanW), before and after a unilateral 4-week isokinetic-concentric training of the dominant DF; to examine the inter-relationships among these isokinetic measures using linear correlation and principal component analysis.

Thirty healthy subjects (26.7±4.6 years old) were randomly assigned to a control or a training group. All dynamometric parameters increased significantly only in the training group for the trained leg ($p<0.05$), with greater gains in work (32-47% at 45°/s and 31-41% at 90°/s) than moment variables (14-18% at 45°/s and 14-28% at 90°/s). Similar increases in strength were also noted at both velocities in the untrained leg ($p<0.01$) for both work and moment parameters, depicting a cross-education effect. Correlations between 'moments' and 'works' increased in both legs after training from 0.59-0.77 to 0.79-0.95. Principal component analysis indicated that, at baseline, PM showed the highest weight on DF performance; after training, meanW at 90°/s and MPM at 45°/s exhibited the highest loadings.

High-intensity training of DF increased the ability in generating energy throughout the entire range of motion rather than maximizing the PM.

2.2 Introduction

Isokinetic dynamometry is considered the reference method for evaluating muscle performance (Dvir, 2004) which can be described in terms of several outcome parameters (Woodson et al., 1995) such as the peak moment (PM), mean peak moment (MPM), maximal work (maxW) and the mean work (meanW). Based strictly on linear correlation analysis, past research has indicated that the PM, also known as peak torque, was highly correlated with the other outcome variables and could efficiently serve as the only representative parameter required for the interpretation of isokinetic data (Woodson et al., 1995; Bandy and Timm, 1992; Morrissey, 1987; Kannus, 1994). However, using principal component analysis (PCA) a recent study has indicated that PM, MPM, maxW and meanW contributed with different weights to ankle dorsiflexors (DF) performance, depending on the angular velocity employed (Manca et al., 2015*a*). The authors have further suggested that in ankle DF, the critical role of PM as the gold standard in isokinetic analysis was well maintained at intermediate angular velocities. However, at lower angular velocities, work measures could complement PM in providing a more comprehensive picture of DF performance. This assumption of complementarity rather than interchangeability of the PM and work supports previous arguments arguing that these parameters were not identical (Kramer and MacDermid, 1989) despite being highly correlated (Dvir and David, 1995).

However, whether the notion of complementarity may be extended to cover different experimental conditions has not been subjected to scientific scrutiny so far. Indeed, past research focused merely on baseline conditions through observational studies (Morrissey, 1987; Kramer and MacDermid, 1989; Bandy and Timm, 1992; Kannus, 1994; Woodson et al., 1995; Dvir and David, 1995; Manca et al., 2015*a*) while none had analysed variations following the administration of a training protocol.

In the light of the above, clinicians should be encouraged to question the independence of these parameters by analyzing their inter-relationships both in physiological and pathological conditions.

Therefore, the objectives of this study were: to bilaterally characterize the performance of ankle dorsiflexion muscles (DF) in terms of PM, MPM, maxW and meanW, before and after a unilateral 4-week isokinetic-concentric training of the dominant DF; to examine the inter-relationships among these isokinetic measures using linear correlation and principal component analysis (PCA), a multivariate statistical technique which allows the retention of the most informative features in data without losing valuable information in the process of reduction analysis (Jolliffe, 2009).

2.3 Methods

2.3.1 Participants

Thirty healthy untrained subjects were recruited among university staff (21 males, 9 females; 26.7±4.6 years old; 70.5±12.0 kg). The demographic characteristics of the participants are reported in Table 1. All participants were requested to avoid any regular sporting or recreational activity during the study. Participants signed an informed consent form. This study (ClinicalTrials.gov identifier: NCT02010398) was conducted in accordance with the Declaration of Helsinki and approved by the local Bioethics Committee of the Local Health Authority (ASL) n.1-Sassari, Italy (ID: Prot. 1160/L).

2.3.2 Study design

This was a parallel-group case-control study in a randomized 1:1 allocation ratio. After baseline evaluation, 30 envelopes were numbered consecutively and randomly assigned to an intervention (Training; *n*=15) or to a no-intervention (Control; *n*=15) group, with a blocking procedure employing Research Randomizer 3.0 software. Testing procedures were performed before (PRE) and after (POST) the experimental period by the same operator at the same time of the day. Both outcome assessors and statistician were blinded to the allocation group. Data were collected in the Department of Biomedical Sciences, University of Sassari (January-December 2014).

2.3.3 Muscle Performance Testing

The primary outcomes, PM, MPM, maxW and meanW, were bilaterally assessed from the ankle DF on an isokinetic dynamometer (Biodex System 3 PRO, Biodex Medical Systems, Shirley, NY, USA) at baseline and within 1 week from the completion of the 4-week intervention. For each subject lower limb dominance was determined according to Hoffman et al. (1998). Before the actual testing participants were familiarized with the dynamometer in a separate session to abate the potential practice-based improvements associated with strength-testing procedures (Dvir and David, 1995). The device was calibrated and assembled with the ankle attachment positioned according to the manufacturer's specifications. The subject was seated with the knee flexed at 30° and the ankle in full plantar flexion as starting position. Gravity compensation was performed. Extraneous body movements were minimized by restraining each subject with shoulder harnesses, hip belts and mid-thigh straps. During the tests subjects' arms were placed across the chest with hands holding on to the straps. Before testing, participants underwent a 5-min warm-up realized by performing 1 set of 6-8 submaximal repetitions at 45 and 90°/s, with a 3-min rest between the 2 angular velocities. After a 5-min rest the criterion test took place and consisted of 4 maximal repetitions at 45°/s and 6 repetitions at 90°/s. The dominant leg was tested first with a 6-min rest between dominant and non-dominant side. No visual feedback or verbal encouragements were provided during testing (Gandevia, 2001). For reproducibility purposes, a retest procedure was executed within 1 week from the initial evaluation.

2.3.4 Intervention protocol

The DF of the dominant leg were arbitrarily chosen to be trained in the intervention group. The training protocol consisted of a 4-week unilateral isokinetic/concentric training, 4 days/week (Monday-Tuesday-Thursday-Friday), with an overall 25-minute duration per session. After a light warm-up subjects performed 3x4 and 3x6 maximal concentric repetitions at 45°/s and 90°/s, respectively, with a 2-min rest between sets. Participants were verbally encouraged during exercise and provided with a visual feedback displaying the real-time moment-angular position curve to motivate the achievement of maximal performance.

2.3.5 Data analysis

STATA 12 (StataCorp, College Station, Texas) was used for the statistical analysis. An *a priori* sample power analysis was performed assuming an expected effect size (Cohen's *d*) of 0.6 and a statistical power of 0.80 at a 0.05 alpha level. For assessing test-retest relative reliability the 2-way random intra-class correlation coefficient for single measures ($ICC_{2,1}$) was performed (Shrout and Fleiss, 1979). Absolute reliability was also estimated with the standard error of measurement (SEM) (Weir, 2005). ICC and SEM scores were assessed separately in women and men to avoid gender-related bias deriving from between-gender strength differences (Almosnino et al., 2012). Sixty measures obtained from the 2 limbs of the 30 subjects were pooled since the coefficient of variation was not different between sides.

Demographic variables were analyzed at baseline with Student *t*-test or Chi-Square test, when appropriate. The Shapiro-Wilk test was used to assess normality. PRE to POST changes at each angular velocity were analyzed with a repeated-measures analysis of variance (ANOVA) with GROUP (training, control) and TIME (PRE, POST) as factors. When significance was achieved, pairwise comparisons with Bonferroni adjustment were used. The smallest real difference (SRD) was calculated to obtain a cut-off value for meaningful training-based gains (Lexell, 2005). Any training-based gain less than the cut-off value was attributed to a measurement error and discarded even if statistically significant. Cohen's *d* effect size magnitudes (small≤0.5; moderate 0.51-0.79; large≥0.8) were also used to quantify differences in the data after intervention.

Linear correlation coefficients (Pearson's *r*) were used to evaluate the degree of linear relationship between all variables with respect to both the PRE- and POST assessments. The PCA was performed at PRE and POST to find the eigenvectors (factors) and eigenvalues. Sampling adequacy was established employing the Kaiser-Meyer-Olkin (KMO) measure (Kaiser, 1970). A scree plot of the eigenvalues associated with each factor was used to determine the number of factors to retain and only those showing eigenvalues greater than 1 were retained. A variable was clearly considered to load on a factor if the loading on the factor was >0.5.

2.4 Results

At baseline the 2 groups were statistically homogeneous for gender, age and weight (Table 1). In all thirty subjects the dominant leg proved to be significantly stronger than the non-dominant leg for all the outcome variables (PM, MPM, maxW and meanW) at 90°/s (all $p<0.05$) and 45°/s (all $p<0.01$). At baseline, no difference in the outcome parameters was detected between groups, in either limbs and at both velocities (Table 2).

Relative and absolute reliability measures (Table 2) indicate high reproducibility of measurements both at 45 and 90°/s, as indicated by ICC coefficients and SEM values, reported only for men, who made the majority of the group (21 out of 30). Regarding women, ICC coefficients were 0.87 at 45°/s and >0.92 at 90°/s, while SEM ranged ±0.5–1.1 at 45°/s and ±0.3–0.8 at 90°/s.

The value of the SRD was 9.8%, rounded conservatively to 10%. As a consequence, any training-based gain <10% was attributed to a measurement error and discarded even if statistically significant.

2.4.1 Changes in muscle performance after training

In the training group significant improvements in muscle performance occurred with high effect sizes (Cohen's *d* >0.9) at both velocities in the trained side (Table 3) as well as in the contralateral untrained side (Table 4). All percent changes were above the 10% SRD value which served as the cut-off to discriminate true meaningful changes from random findings.

Greater gains were recorded for the work-related (maxW and meanW) compared to the moment-related (PM and MPM) outcome parameters in the trained side: 31-41% *versus* 14-28%, at 90°/s, and 32-47% *versus* 14-18% at 45°/s, respectively. In the untrained side, these improvements were even higher: 34-39% *versus* 26-27% at 90°/s, and 48-53% *versus* 11-20%, at 45°/s, respectively. No parallel significant gains were detected for any of the parameters in the control group. Significant main effects and interactions were found and detailed in Table 5.

2.4.2 Linear correlation analysis

Correlation analysis showed that all variables (PM, MPM, maxW and meanW) were significantly associated ($p<0.0001$). PRE to POST changes in correlations between all pairs of variables, expressed as Pearson's r coefficients, are outlined in Table 6 by group, side and angular velocity.

At baseline the correlations between moment (PM *versus* MPM) and work (maxW *versus* meanW) parameters showed the highest correlation coefficients (0.74-0.97) at both velocities. However, the correlations between moment and work measures were only fair-to-good (0.59-0.77). Following training, an increase in the magnitude of the coefficients, both in the trained and untrained limb, was observed for all variables, particularly between moment and work measures at both velocities. By contrast, in the control group no parallel changes were observed. The correlation between PM and maxW, chosen as representative of the relationships between all variables which followed the same pattern, is graphically displayed at 90 (Figure 1) and 45°/s (Figure 2) for the training group.

2.4.3 Principal component analysis

Only the first principal component of the total variance showed an eigenvalue >1 and was therefore extracted. The component extracted accounted for the largest amount of total variance in percentage (81% at 90°/s and 83% at 45°/s). The loading factors onto the first principal component were detected by the one-dimensional representation which showed changes in the contributions to muscle performance of each considered variable from PRE- to POST assessments at both angular velocities (Figures 3 and 4).
In both groups at the PRE assessment, the weights of moment and work parameters onto the component 1 were different, depending on the angular velocity. The training group exhibited remarkable PRE to POST variations in loading factors as well as in the hierarchy of contributions of PM, MPM, maxW and meanW to muscle performance (Figures 3a and 4a). These variables appeared clearly scattered at baseline while gathered and packed around the cut-off value of 0.5 after training in the trained (Figure 3) and untrained (Figure 4) legs. On the other hand the control group evidenced no variation in the general pattern of distribution of the variables (Figure 3b and 4b).

2.5 Discussion

The present study characterized dynamometric parameters contributing to muscle performance of ankle DF in physiological baseline conditions and explored how resistance training of such muscles influenced the relationships among the isokinetic variables under scrutiny.

2.5.1 Training-induced changes in muscle performance

PM, MPM, maxW and meanW significantly increased in the trained and untrained DF muscles after a 4-week maximal-intensity training of the dominant leg. SRD and SEM scores indicate that these changes are to be considered true rather than random findings. Changes in dynamometric parameters observed in the trained muscles following high-intensity training were expected (Heggelund et al., 2013). Work measures exhibited greater gains than moments at 90°/s (31-41% *versus* 14-28%) and 45°/s (32-47% *versus* 14-18%), as previously described (Manca et al., 2015*b*). These data suggest that maximal-intensity training of the DF exerts a higher impact on 'works' than 'moments' at both angular velocities.

A concomitant increase in these measures in the untrained side was expected as well, consistently with the occurrence of a cross-education phenomenon, *i.e.* the performance improvement in the untrained limb after training of the contralateral side (Zhou, 2000; Munn et al., 2004). Strength increases were greater in the untrained than trained leg, both in terms of work and moment measures. These findings are surprising since it is generally accepted that the gain of strength in the untrained limb is a 25-50% of that in the trained one (Zhou, 2000; Munn et al., 2004). Such apparently striking results may be explained by the high-intensity feature of the exercise employed in this study which highly impacts on neural factors considered responsible for the cross-education effect (Enoka, 1997; Zhou, 2000; Munn et al., 2004; Hortobágyi, 2005). Similar findings have been previously reported in the upper limbs where the preferential direction from dominant to non-dominant side has been accounted for the asymmetric response of the 2 limbs to training (Farthing et al., 2007). However, this might not apply to lower limbs where dominance is still controversial (Gentry and Gabbard, 1995). The physiological strength asymmetry between the 2 legs here observed at baseline might account for the proportionally higher response of the non-dominant ("weaker") leg to training, since it may have wider margins for changes than the dominant ("stronger") leg. Although isolated dorsiflexion employed in our protocol is a relatively simple motor task, we

hypothesize that the occurrence of the cross-education effect may have occurred not only as a transfer of strength but also of motor skills in terms of optimal strategy to execute a maximal dorsiflexion against resistance along the isokinetic range of motion.
It is noteworthy that the estimation of the magnitude of the training-induced improvements in muscle performance should take into proper account the familiarization/learning-effect, which is a serious concern in strength testing (Dvir and David, 1995). We are confident that the results were not substantially affected by the familiarization effect, since in DF muscles its magnitude was estimated as a non-significant 0.2-2.1% increase in PM and 9.8-11% in maxW, depending on the angular velocity (Manca et al., 2015*b*).

2.5.2 Linear correlation

After training the correlation between moment and work measures increased from *fair-to-good* (*r*=0.59-0.77) to *very high* (*r*=0.79-0.95), at 45 and 90°/s. These data on the relationship between PM and maxW in baseline conditions are consistent with previous reports (Woodson et al., 1995; Bandy and Timm, 1992; Morrissey, 1987; Kannus, 1994; Dvir and David, 1995; Kramer and MacDermid, 1989), while changes in correlation coefficients following training have not been addressed before. Remarkably, in the intervention group, the variation in linear coefficients calculated for the untrained DF followed the same pattern as the directly trained muscles. This is the first evidence of the occurrence of the cross-education phenomenon not only in terms of strength changes in the untrained limb but also as modifications in the relationships between variables contributing to the ‘cross-transferred’ muscle performance. Notably, the correlations PM *versus* MPM and maxW *versus* meanW were unchanged after training, probably due to a ceiling effect, being their Pearson’s *r* coefficients very high in baseline conditions already.

2.5.3 Principal component analysis

The PCA approach proved well-suited to outline a hierarchical ranking among the 4 independent dynamometric variables here considered, allowing the retention of the most informative parameters describing the ankle DF muscle performance. To this regard, the loading factors of PM, MPM, maxW and meanW were employed to weigh their relative contributions to muscle performance. Our PCA-based data evidence that these parameters contribute to muscle performance of DF with different weights at baseline and that their loadings are remarkably influenced by training. In more detail, at 90°/s, PM showed the highest loading on muscle performance at baseline, thus being the parameter best explaining its variability in this condition, consistently with a previous PCA study (Manca et al., 2015*a*) and other reports based on linear correlation analysis (Woodson et al., 1995; Bandy and Timm, 1992; Morrissey, 1987; Kannus, 1994; Dvir and David, 1995; Kramer and MacDermid, 1989). After the intervention, the pattern of contributions of each variable to muscle performance changed, so that meanW was its best contributor, suggesting that high-intensity training may impact more on work than moment measures, in line with the observed percent changes in muscle performance (see above). At 45°/s the hierarchy of contributions was different in the 2 limbs of the training group: in the dominant trained leg PM proved to be the best determinant of muscle performance both at the PRE- and POST-assessments; in the non-dominant untrained leg the highest loadings were exhibited by MPM and PM at baseline and only by MPM after intervention. These different patterns suggest that the 2 legs may adopt different strategies which can be viewed in the perspective of the different roles they play while executing a motor task. In fact, it has been shown that the dominant and non-dominant lower limbs are differently specialized, with the former more involved in mobility and the latter in stability (Gentry and Gabbard, 1995).

The above findings indicate that PM, MPM, maxW and meanW are not interchangeable in line with previous studies (Dvir and David, 1995; Kramer and MacDermid, 1989) and in disagreement with other reports which acknowledged PM as the only parameter worthy to be retained (Bandy and Timm, 1992; Woodson et al., 1995).

2.5.4 Response of dynamometric variables to high-intensity exercise

The morphological variations detected by the correlation scatterplots as well as in the PCA loading plots evidenced a dynamic behavior of PM, MPM, maxW and meanW in response to maximal resistance training. In the training group these variables moved from PRE- to POST in a *scatter-to-gather* fashion, while no variation was detected in the controls in terms of ranking and/or morphological properties of their one-dimensional representation. This *scatter-to-gather* trend confirms that dynamometric parameters contribute differently to muscle performance (Manca et al., 2015*a*) depending on external conditions such as the angular velocity employed or the training administered. Notably, in the training group and with respect to both velocities, all variables showed a tendency to gather operating at the trained as well as the untrained sides and supporting the occurrence of the cross-education effect.

With specific regard to the lower angular velocity (45°/s), a different bilateral pattern of behavior was revealed in baseline conditions with variables showing a more packed distribution around the cut-off value of 0.5 in the dominant side and a clearly dispersed distribution in the contralateral leg. In particular, at baseline the work-related variables of the non-dominant DF contributed to muscle performance to a lesser extent than moments, compared to the dominant DF where all variables exhibited almost equal loadings, thus exerting quite similar weights on muscle performance. This discrepancy tended to diminish after the intervention since the bilateral distribution of the dynamometric variables became more symmetrical and packed around the cut-off value. After training, loadings exerted by work measures converged to the critical 0.5 cut-off value, further confirming that lower angular velocity training affected work- more than moment-related measures. These assumptions should be cautiously generalized to muscle groups other than ankle DF, since the tibialis anterior, which is the main muscle of this group, is considered peculiar from the neurophysiological and biomechanical point of view (Tallent et al., 2013). However, this muscle group was chosen as a model for this study due to its susceptibility and resulting severe disability in many neurological disorders (Sackley et al., 2009). Despite the unique role of ankle DF in human locomotion and the relevant clinical implications of their impairment, only a few reports were focused on these muscles both in physiological (Uh et al., 2000; Dragert and Zehr, 2011) and pathological (Dragert and Zehr, 2013) conditions and none evaluated the effects induced by their training not only in terms of moment- but also of work-related measures. The results of this study indicate that work and moment parameters are complementary rather than interchangeable in providing a more comprehensive picture of muscle performance. This may prove of potential interest in both sports science and rehabilitative scenarios. Thus, a comprehensive assessment of both “moments” and “works” may prove useful in rehabilitative settings, particularly in neurological disorders and early phases of orthopedic conditions where the employment of specific velocities of muscle contractions is indicated.

Moreover, incorporating SEM and SRD analyses in the interpretation of isokinetic findings may help identify those training-induced changes that are functionally and/or clinically meaningful. The present study provides evidence that ‘works’ are more responsive than ‘moments’ to maximal-intensity training of ankle DF. Thus, meaningful changes are more likely to be detected by the work done throughout the entire range of motion than by the PM which is a single point over the entire isokinetic curve.

2.6 Conclusions

Moment and work variables capture different aspects of muscle performance and contribute to it with different loadings in baseline conditions, depending on the angular velocity. More importantly, their weights on muscle performance as well as their mutual relationships exhibit different responsiveness to resistance exercise. In this regard, while the PM remains the gold standard parameter at baseline or single test conditions, work-related measures show higher responsiveness and sensitivity to maximal isokinetic concentric resistance training. This concept is crucial in the framework of strength testing and training for the valid interpretation of the findings, since considering the most informative variables is essential in order to properly describe the phenomena under investigation without neglecting *a priori* useful parameters.

2.7 Table And Figure

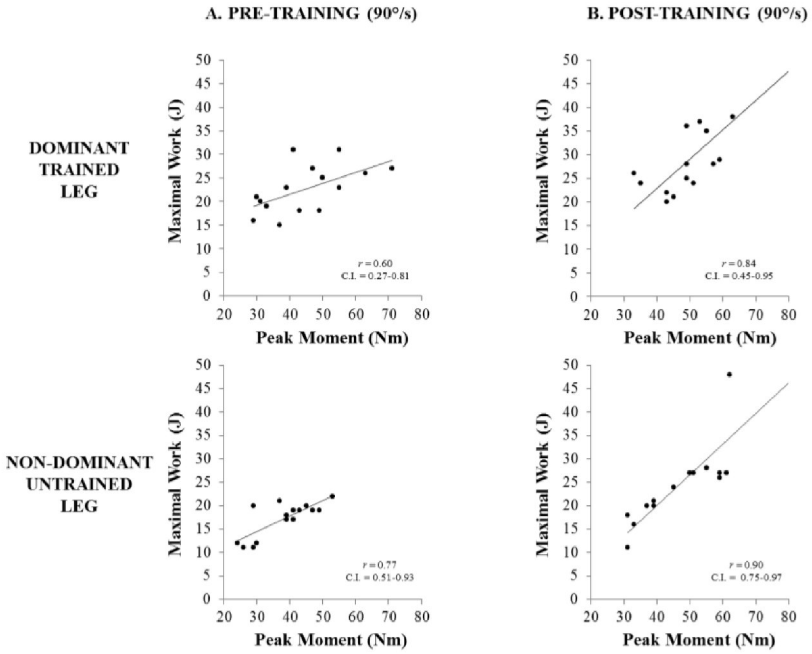


Figure 1. Scatterplots showing correlations by side, at baseline (PRE) and after training (POST) between peak moment and maximal work at 90°/s of angular velocity, in the training group.

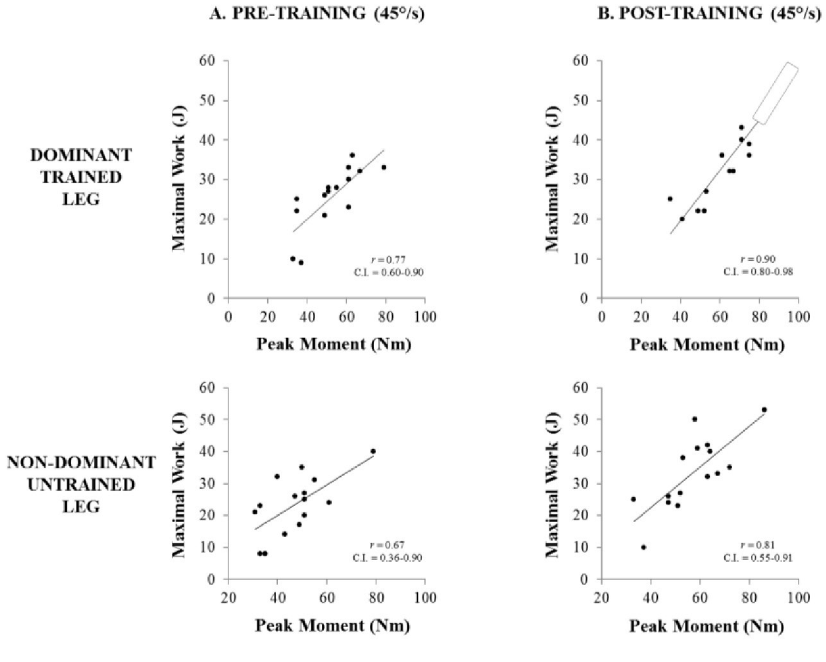


Figure 2. Scatterplots showing correlations, by side, at baseline (PRE) and after training (POST) between peak moment and maximal work at 45°/s of angular velocity, in the training group.

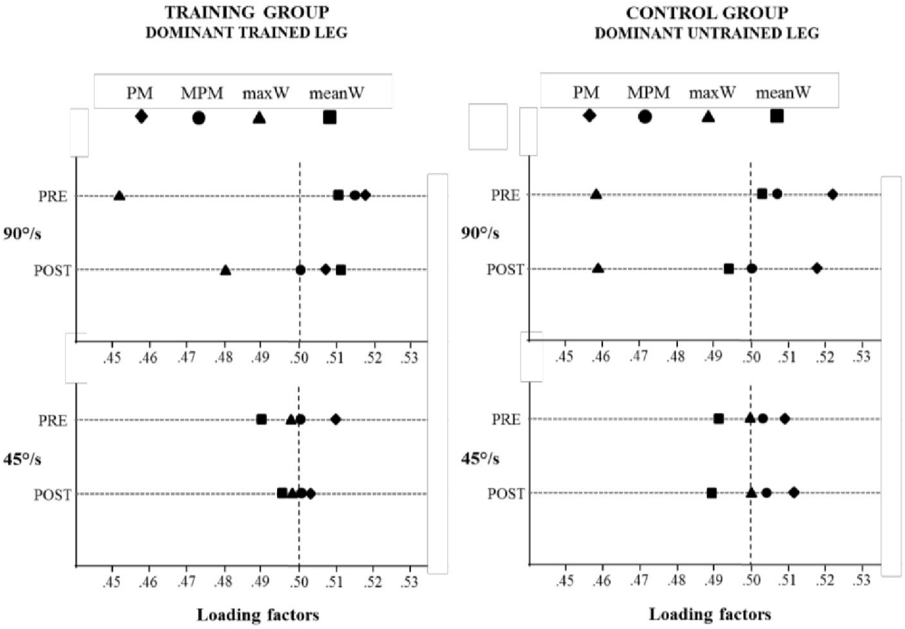


Figure 3. Loading plots of muscle performance variables at 90 and 45°/s. Data obtained from the dominant trained ankle dorsiflexion muscles are reported: A) for the trained group (n= 15 subjects) at baseline (PRE) and after a 4-week training (POST) and (B) for the control group (n= 15 subjects) at baseline (PRE) and after a 4-week period of no-intervention (POST). PM = peak moment; MPM = mean peak moment; maxW = maximal work; meanW = mean work.

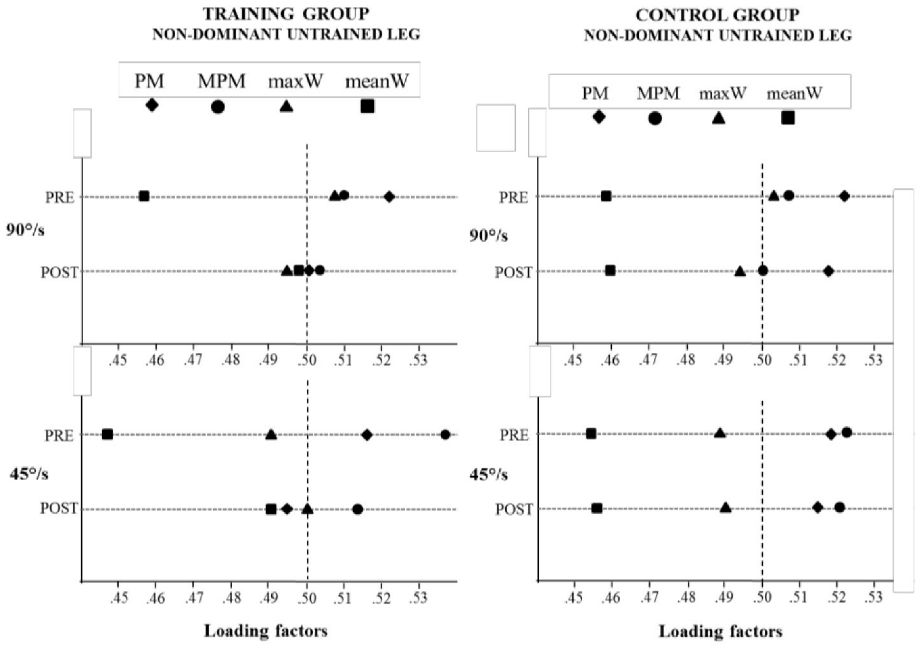


Figure 4. Loading plots of muscle performance variables, at 90 and 45°/s. Data obtained from the non-dominant untrained left ankle dorsiflexion muscles are shown A) for the trained group (*n*=15 subjects), at baseline (PRE) and after a 4-week training (POST) and (B) for the control group (n= 15 subjects) at baseline (PRE) and after a 4-week period of no-intervention (POST). PM = peak moment; MPM = mean peak moment; maxW = maximal work; meanW = mean work.

Table 1. Demographic characteristics of the participants at baseline.

Demographic features	Training Group (*n* = 15)	Control Group (*n* = 15)	Statistics
Age (years) *95% CI*	25.7 ± 5.4 *22.7 – 28.7*	27.7 ± 3.7 *25.6 – 29.7*	$F_{1,29}$ = 1.42; $p = 0.24$
Gender (%)	F: 5 (33.3%) M: 10 (66.7%)	F: 4 (36.4%) M: 11 (63.6%)	Pearson's $\chi2$: $p = 0.5$
Weight (kg) *95% CI*	67.1 ± 13.0 *59.9 – 74.3*	73.9 ± 10.2 *68.3 – 79.5*	$F_{1,29}$ = 2.58; $p = 0.12$

CI = Confidence Interval; F = Females; M = Males

Table 2. Reproducibility of isokinetic outcome measures obtained from the dominant and non-dominant ankle dorsiflexors in male subjects ($n = 21$).

Angular velocity	Variables	Dominant ankle DF muscles				Non-dominant ankle DF muscles			
		Day 1 (test)	Day 2 (retest)	ICC (95% C.I.)	SEM (Nm)	Day 1 (test)	Day 2 (retest)	ICC (95% C.I.)	SEM (Nm)
90°/s	PM (Nm)	44.0±7.5	45.2±7.3	0.86 (0.70-0.94)	±4.0	39.4±6.5	40.6±6.6	0.87 (0.74-0.96)	±3.2
	MPM (Nm)	37.2±6.7	39.4±7.3	0.94 (0.86-0.97)	±2.1	34.9±5.8	36.6±6.3	0.93 (0.84-0.97)	±2.1
	maxW (J)	18.7±5.8	20.6±5.7	0.93 (0.83-0.97)	±1.5	17.0±3.4	18.8±4.3	0.87 (0.70-0.94)	±1.9
	meanW (J)	14.3±4.4	16.0±4.7	0.96 (0.92-0.99)	±1.1	14.0±4.9	15.1±5.6	0.92 (0.81-0.97)	±1.7
45°/s	PM (Nm)	50.7±9.1	53.5±10.3	0.97 (0.93-0.99)	±2.1	47.2±9.5	50.2±10.6	0.98 (0.95-0.99)	±1.7
	MPM (Nm)	42.9±9.7	45.7±10.0	0.96 (0.90-0.98)	±2.4	40.6±9.5	43.5±9.4	0.96 (0.91-0.98)	±2.3
	maxW (J)	23.5±6.7	24.5±7.2	0.99 (0.97-0.99)	±0.8	22.6±8.0	23.8±8.2	0.98 (0.94-0.99)	±1.1
	meanW (J)	20.1±6.9	21.1±7.8	0.95 (0.87-0.98)	±1.0	17.9±6.5	19.5±6.9	0.98 (0.95-0.99)	±1.0

PM = peak moment; MPM = mean peak moment; maxW = maximal total work; meanW = mean total work; Nm =Newton*meter; J=joules; °/s=degrees/second of isokinetic angular velocity; Test=assessment performed at baseline; Retest=assessment performed within one week from baseline; $\text{ICC}_{2,1}$=intra-class correlations for test-retest comparison; 95% C.I.=Confidence Interval at 95%; SEM=standard error of measurements.

Table 3. PRE to POST changes in muscle performance of the dominant dorsiflexors.

Angular velocity	Dynamometric Variables	Training Group ($n = 15$)			Control group ($n = 15$)		
		PRE	POST	% Change	PRE	POST	% Change
90°/s	PM (Nm)	44.9±12.5	51.3±12.7	+14.2*	38.7±7.4	40.3±7.8	+4.1
	MPM (Nm)	36.27±8.5	46.7±13.4	+28.7***	33.5±6.7	34.3±7.5	+2.4
	maxW (J)	22.7±7.7	29.9±9.3	+31.7***	18.6±6.0	20.0±4.7	+7.5
	meanW (J)	17.8±3.8	25.2±9.3	+41.6**	16.2±3.5	16.8±4.1	+3.7
45°/s	PM (Nm)	52.5±13.8	62.2±15.5	+18.5***	44.4±9.7	44.6±10.8	+0.4
	MPM (Nm)	42.8±11.9	48.8±13.2	+14.0***	39.9±8.9	42.3±9.1	+6.0
	maxW (J)	25.5±7.8	33.7±10.9	+32.1**	21.6±6.0	21.8±5.8	+0.9
	meanW (J)	20.3±7.3	29.9±9.9	+47.3***	21.0±7.6	22.2±11.4	+5.7

Dominant limb = trained limb in the Training group and untrained limb in the Control group; PRE = values at baseline assessment; POST = values at the assessment performed after a 4-week maximal intensity training; PM = peak moment; MPM = mean peak moment; maxW = maximal total work; meanW = mean total work; Nm =Newton*meter; J=joules; *Significant for $p<0.05$; **significant for $p<0.01$; ***significant for $p<0.0005$.

Table 4. PRE to POST changes in muscle performance of the non-dominant ankle dorsiflexors.

Angular velocity	Dynamometric Variables	Training Group (*n* = 15)			Control group (*n* = 15)		
		PRE	POST	% Change	PRE	POST	% Change
90°/s	PM (Nm)	38.3±7.5	48.9±14.9	+27.7**	37.4±9.5	37.5±9.3	+0.3
	MPM (Nm)	34.1±7.3	43.1±13.4	+26.4**	33.1±8.4	33.6±7.1	+1. 5
	maxW (J)	18.8±4.4	26.2±11.1	+39.4**	15.3±5.4	16.8±5.4	+9.8
	meanW (J)	15.5±6.1	20.9±10.3	+34.8**	13.5±5.0	14.3±4.9	+5.9
45°/s	PM (Nm)	47.3±12.5	56.8±13.5	+20.0***	42.7±11.7	43.6±12.3	+2.1
	MPM (Nm)	45.5±11.9	53.5±12.8	+11.1***	38.3±12.7	40.1±13.6	+4.7
	maxW (J)	22.5±8.1	33.3±11.2	+48.0***	18.1±8.3	20.1±8.3	+11.0
	meanW (J)	18.3±4.1	28±10.6	+53.0***	16.4±6.6	17.3±6.9	+5.5

Non-dominant limb = untrained limb in both Training and Control groups. PRE = values at baseline assessment; POST = values at the assessment performed after a 4-week maximal intensity training; PM = peak moment; MPM = mean peak moment; maxW = maximal total work; meanW = mean total work; Nm =Newton*meter; J=joules; 90°/s and 45°/s = values of isokinetic angular velocities. *Significant for $p<0.05$; **significant for $p<0.01$; ***significant for $p<0.0005$.

Table 5. Main effects and interactions as tested by repeated measures analysis of variance (*n* = 30).

Angular velocities	Main effects and interactions	PM (Nm)		MPM (Nm)		maxW (J)		meanW (J)	
		Dominant	Non-dominant	Dominant	Non-dominant	Dominant	Non-dominant	Dominant	Non-dominant
90°/s	Time	F=27.87 p<0.0005	F=13.66 p=0.001	F=32.73 p<0.0005	F=13.48 p=0.001	F=13.92 p<0.0005	F=19.04 p<0.0005	F=15.16 p=0.001	F=10.45 p=0.003
	Group	F=5.91 p=0.02	F=2.45 p=0.13	F=5.24 p=0.03	F=2.75 p=0.10	F=20.44 p<0.0005	F=7.03 p=0.01	F=15.75 p=0.001	F=7.55 p=0.01
	Time x Group	F=9.06 p=0.006	F=14.82 p=0.0002	F=7.64 p=0.01	F=18.57 p<0.0005	F=10.31 p=0.006	F=10.36 p=0.004	F=13.08 p=0.001	F=9.34 p=0.005
45°/s	Time	F=27.18 p=0.0005	F=22.96 p<0.0005	F=30.95 p<0.0005	F=18.02 p<0.0005	F=21.06 p<0.0005	F=25.09 p<0.0005	F=17.24 p<0.0005	F=17.51 p<0.0005
	Group	F=7.28 p=0.01	F=4.64 p=0.04	F=8.46 p=0.007	F=7.11 p=0.01	F=6.45 p=0.02	F=7.40 p=0.01	F=5.89 p=0.02	F=9.32 p=0.005
	Time x Group	F=28.93 p<0.0005	F=24.97 p<0.0005	F=32.06 p<0.0005	F=19.36 p<0.0005	F=9.41 p=0.005	F=24.43 p<0.0005	F=12.87 p=0.002	F=15.31 p=0.001

PM = peak moment; MPM = mean peak moment; maxW = maximal total work; meanW = mean total work; Nm =Newton*meter; J=joules; dominant (stronger) limb = trained limb in the training group and untrained limb in Control group; non-dominant (weaker) limb = untrained limb in both groups.

2.8 References

1. Almosnino S, Stevenson JM, Bardana DD, Diaconescu ED and Dvir Z. Reproducibility of isokinetic knee eccentric and concentric strength indices in asymptomatic young adults. Phys Ther Sport 2012;13(3):156-62.
2. Bandy WD and Timm KE. Relationship between peak torque, work, and power for knee flexion and extension in clients with grade I medial compartment sprains of the knee. J Orthop Sports Phys Ther 1992;16(6):288-92.
3. Dragert K and Zehr EP. Bilateral neuromuscular plasticity from unilateral training of the ankle dorsiflexors. Exp Brain Res 2011;208(2):217-27.
4. Dragert K and Zehr EP. High-intensity unilateral dorsiflexor resistance training results in bilateral neuromuscular plasticity after stroke. Exp Brain Res 2013;225(1):93-104.
5. Dvir Z. Isokinetics: Muscle Testing, Interpretation and Clinical Applications. 2nd ed, Edinburgh, Churchill Livingstone, 2004
6. Dvir Z and David G. Average or peak moment: Which of the 2 is more suitable to represent isokinetic muscle strength? Isokinetics Exerc Sci 1995;5(2):93-7.
7. Enoka RM. Neural adaptations with chronic physical activity. J Biomech 1997;30(5):447-55.
8. Farthing JP, Borowsky R, Chilibeck PD, Binsted G and Sarty GE. Neuro-physiological adaptations associated with cross-education of strength. Brain Topogr 2007;20(2):77-88.
9. Fimland MS, Helgerud J, Solstad GM, Iversen VM, Leivseth G and Hoff J. Neural adaptations underlying cross-education after unilateral strength training. Eur J Appl Physiol 2009;107(6):723-30.
10. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev 2001;81(4):1725-89.

11. Gentry V and Gabbard C. Foot-preference behavior: a developmental perspective. J Gen Psychol 1995;122(1):37-45.
12. Heggelund J, Fimland MS, Helgerud J and Hoff J. Maximal strength training improves work economy, rate of force development and maximal strength more than conventional strength training. Eur J Appl Physiol 2013;113(6):1565-73.
13. Hoffman M, Schrader J, Applegate T and Koceja D. Unilateral postural control of the functionally dominant and nondominant extremities of healthy subjects. J Athl Train 1998;33(4):319-22.
14. Hortobágyi T. Cross education and the human central nervous system. IEEE Eng Med Biol 2005;24(1):22-28.
15. Jolliffe IT. Choosing a Subset of Principal Components or Variables. In: Jolliffe IT, Principal Component Analysis. 2nd edn, New York, Springer Verlag, 2009.
16. Kaiser HF. A second generation Little Jiffy. Psychometrika 1970;35, 401-16.
17. Kannus P. Isokinetic evaluation of muscular performance: Implications for muscle testing and rehabilitation. Int J Sports Med 1994;15(1):11-18.
18. Kidgell DJ, Stokes MA and Pearce AJ. Strength training of one limb increases corticomotor excitability projecting to the contralateral homologous limb. Motor Control 2011;15(2):247-66.
19. Kramer JF and MacDermid J. Isokinetic measures during concentric-eccentric cycles of the knee extensors. Aust J Physiother 1989;35(1):9-14.
20. Lexell JE and Downham DY. How to assess the reliability of measurements in rehabilitation. Am J Phys Med Rehabil 2005;84(9):719-23.
21. Manca A, Solinas G, Dragone D and Deriu F. Isokinetic testing of muscle performance: new concepts for strength assessment. Isokinet Exerc Sci 2015*a*;DOI 10.3233/IES-15-566.
22. Manca A, Pisanu F, Ortu E, De Natale ER, Ginatempo F, Dragone D, Tolu E and Deriu F. A comprehensive assessment of the cross-training effect in ankle dorsiflexors of healthy subjects: a randomized controlled study. Gait and Posture 2015*b*; DOI 10.1016/j.gaitpost.2015.04.005.

23. Morrissey MC. The relationship between peak torque and work of the quadriceps and hamstrings after meniscectomy. J Orthop Sports Phys Ther 1987; 8(8):405-8.
24. Munn J, Herbert RD and Gandevia SC. Contralateral effects of unilateral resistance training: A meta-analysis. J Appl Physiol 2004;96(5):1861-66.
25. Sackley C, Disler PB, Turner-Stokes L, Wade DT, Brittle N and Hoppitt T. Rehabilitation interventions for foot drop in neuromuscular disease. Cochrane Database Syst Rev 2009;8;(3):CD003908.
26. Shrout PE and Fleiss JL. Intraclass correlation: uses in assessing rater reliability. Psychol Bull 1979;86(2):430-28.
27. Tallent J, Goodall S, Hortobágyi T, St Clair Gibson A and Howatson G. Corticospinal responses of resistance-trained and un-trained males during dynamic muscle contractions. J Electromyogr Kinesiol 2013;23(5):1075-81.
28. Uh B, Beynnon BD, Helie BV, Alosa DM and Renstrom PA. The benefit of a single-leg strength training program for the muscles around the untrained ankle: A prospective, randomized, controlled study. Am J Sports 2000; Med 28(4):568-73.
29. Weir JP. Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. J Strength Cond Res 2005;19(1):231-40.
30. Woodson C, Bandy WD, Curis D and Baldwin D. Relationship of isokinetic peak torque with work and power for ankle plantar flexion and dorsiflexion. J Orthop Sports Phys Ther 1995;22(3):113-15.
31. Zhou S. Chronic neural adaptations to unilateral exercise: Mechanisms of cross education. Exerc Sport Sci Rev 2000; 28(4):177-84.

Study 3: A comprehensive assessment of the Cross-training effect in ankle dorsiflexors of healthy subjects: a randomized controlled study

3.1 Abstract

Purpose: to investigate the Cross-Training effect, induced on ankle dorsiflexors (AD) by unilateral strength-training of the contralateral muscles, as transfer of peak torque (PT) and muscle work (MW) and their relative contributions to muscle performance.

Methods: Thirty healthy volunteers were randomly assigned to a training or control group. The trained group sustained a 4-week maximal isokinetic training of the stronger AD at 90 and 45°/s. At both angular velocities, PT, MW and MW/PT ratio were measured from both legs at baseline and after intervention (trained group) or no-intervention (controls). The familiarization/learning-effect was calculated and subtracted by PT and MW measures to obtain their net changes.

Results: Net PT increased in both legs (untrained: +27.5% at 90°/s and +17.9% at 45°/s; trained: +15% at 90°/s and +16.3% at 45°/s). Similarly, net MW increased in both the untrained (90°/s: +29.6%; 45°/s: +37%) and trained (90°/s: +23.4%; 45°/s: +18.3%) legs. PT and MW gains were larger in the untrained than trained AD ($p<0.0005$), with MW improving more than PT at 45°/s ($p=0.04$). The MW/PT ratio increased bilaterally only in the trained group ($p<0.05$), depending on the angular velocity.

Conclusions: The Cross-training effect occurred in AD muscles in terms of both PT and MW, with MW adding valuable information to PT-analysis in describing muscle performance. Moreover, the MW/PT ratio allowed estimating the contributions of these parameters to muscle capability and may represent a novel index in isokinetic testing. The greater improvements in the untrained than trained limb raises interesting clinical implications in asymmetric conditions.

ClinicalTrials.gov identifier: NCT02010398

3.2 Introduction

The Cross-Training (CT) effect, also known as “cross-education” and “cross-transfer”, is the performance improvement in the untrained limb following a period of training of the contralateral side. A 5-25% magnitude of strength transfer has been described [1], with an average increase of maximal strength in the untrained side of 7.8%, which is approximately 25-50% of the gain on the trained side [2]. Higher transfers have been described when training is administered through eccentric contractions or in conjunction with electrical muscle stimulation [3]. Differences in the trials design and/or training protocols employed may be responsible for the variability of the results [2].

Physiological mechanisms underlying the CT effect are still poorly understood. Morphological or enzymatic changes in the untrained muscles were undetected while neural adaptations occurring at multiple sites within the central nervous system have been advocated as contributors to the CT phenomenon [2,4-7].

Overall, CT studies have focused merely on parameters describing maximal strength, mainly the isokinetic peak torque (PT) and the isometric maximal voluntary contraction. Curiously, no data are currently available about the transfer of performance in terms of muscle work (MW), despite PT and MW provide quite different information. While PT is an instantaneous measure of strength exerted at one single point, MW is the average measure of the torque output throughout the entire range of motion [8]. In addition, when assessing muscle strength, research has shown that average moments, represented also through MW, are more appropriate than peak ones [9], and, in a rehabilitative perspective, MW is considered a better indicator of the function of a muscle group than PT since, in real-world environments, muscles need to maintain the force outputs over time and over distance [8]. By contrast, a number of relevant isokinetic studies proposed PT and MW as interchangeable parameters in describing muscle strength [11-13]. These studies based on linear correlation analyses which revealed high coefficients between PT and MW, thus confirming the general idea that PT may be the only necessary parameter to be recorded. The discrepancy between these positions raises issues on the role played by each of the two variables contributing to muscle performance, as well as on their mutual relationship.

Concerning the body districts investigated in CT research, studies equally cover the upper, mainly wrist and elbow muscles, and lower extremities, particularly knee flexors/extensors and ankle plantarflexors [1,2]. Pooled data have shown that the CT-induced transfer occurs to a higher extent in the lower (10.4%) than upper (3.8%) limbs [2].

Only a few studies, using different paradigms, have dealt with the CT-effect in the ankle dorsiflexors (AD), namely the tibialis anterior (TA) muscle [14-16] and none has investigated the crossed gain in these muscles in a more comprehensive manner, *i.e.* not only in terms of PT but also of MW. This seems surprising considering the unique role of TA in human locomotion and clinical implications of its impairment. Moreover, such lack of data may have contributed to an underestimation of the full potential of CT as a rehabilitative strategy for unilateral weakness conditions, as suggested by the fact that CT efficacy in TA of stroke patients has been investigated only very recently [17].

The present study tested the hypothesis that a unilateral training of AD muscles of healthy subjects would result in: *i)* a contralateral increase in strength not only in terms of PT but also of MW; *ii)* a variation in their contributions to muscle performance expressed as MW/PT ratio, which is here presented for the first time as a tool for evaluation of the mutual relationship between these variables.

3.3 Methods

3.3.1 Participants

Thirty healthy volunteers (21 males, 9 females; 26.7±4.6 years old; 70.5±12.0 kg) participated in this study conducted between September 2013-May 2014 at the Department of Biomedical Sciences of the University of Sassari in accordance with the Declaration of Helsinki after approval by the Bioethics Board of ASL n.1-Sassari, Italy (ID:1160/L). After signing an informed consent, all participants underwent a screening for orthopedic/neurological conditions and were enrolled by FP and ERDN. Subjects were asked to refrain from any other exercise activity for the entire duration of the study. Participation in any sporting activity on a regular basis, even recreational, was set as a criterion of exclusion.

3.3.2 Trial design and protocol

Design was set as a parallel-group case-control study in a randomized 1:1 allocation ratio. Subjects underwent dynamometric assessment before (PRE) and after (POST) a period of training or no-intervention, depending on the group of assignment. Once baseline evaluation was completed, 30 envelopes were numbered consecutively by EO and randomly assigned to an intervention (CT; *n*=15) or to a control group (*n*=15) with a blocking procedure employing Research Randomizer 3.0 software [18]. Both outcome assessors and statistician were blinded to the allocation group.

3.3.3 Muscle Performance Testing

Muscle performance of AD muscles was unilaterally tested for both legs on an isokinetic dynamometer (Biodex System 3, NY, USA). The experimental set up is shown in Figure 1. The subject was positioned in the modified seated position according to Backman and Oberg (1989) with the knee flexed at 30° and the ankle in full plantar flexion taken as starting position [19]. The ankle joint range of motion was recorded and kept constant from PRE-POST. The position of the ankle was firmly secured to the dynamometer with supplied straps. Extraneous body movements were minimized by restraining each subject with shoulder harnesses, a hip belt, a mid-thigh restraint strap and two ankle straps. Prior to the testing protocol, all subjects received the instruction "pull up hard as fast as you can" with the tested leg while keeping the contralateral one relaxed. In a separate session, participants became familiar with the isokinetic device to minimize the potential effects of learning associated to testing procedures [4]. For each subject lower limb dominance was determined through a battery of functional tests [20]. The dominant leg was tested first. All subjects underwent a predefined 5-minute warm-up by performing one set of six-to-eight submaximal repetitions at 45°/s and 90°/s angular velocities, with a 2-to-3-minute rest in between. After 5 minutes, PT and maximal MW for the best repetition were unilaterally recorded from both legs, with a 6-minute rest given in between. No feedback or verbal encouragements were provided to the subject during testing, to avoid any bias deriving from the operator-subject interaction [21]. The intra-machine reliability of the isokinetic device and the reproducibility of measurements were estimated performing a retest procedure within one week from the initial assessment. MW/PT ratio was also calculated at 90°/s and 45°/s.

3.3.4 Intervention

Only the CT group sustained an exercise program consisting of a 4-week unilateral isokinetic/concentric training of the stronger AD, four days per week (Monday-Tuesday-Thursday-Friday), 25-minutes per session. A maximal-intensity regimen was employed to impact on the nervous factors mediating maximal strength capacity [22,23]. When a session was missed, subjects were allowed to recover it at the end of the cycle. Training was performed on the same isokinetic dynamometer used for the testing. After a light warm-up (see above), subjects sustained three sets of 4 maximal repetitions at 45°/s and three sets of 6 maximal repetitions at 90°/s, in accordance with the established *modus operandi* in isokinetics, where slow speed protocols are generally conducted with a minor number of repetitions than faster speeds [10]. A 2-minute rest was given between sets. To stimulate achieving the maximal performance, participants were verbally encouraged during exercise and provided with a visual feedback displaying the real-time strength output.

3.3.5 Contralateral transfer of strength and muscle work

To control and estimate the familiarization/learning-effect, which has been shown as an issue in previous CT studies, the equation by Carroll et al. [4] was employed to determine the difference in PRE-POST changes in muscle performance of the untrained leg in the two groups

$$\left[\frac{E_{POST} - E_{PRE}}{E_{PRE}} - \frac{C_{POST} - C_{PRE}}{C_{PRE}}\right]100$$

where E_{POST} refers to mean POST-training PT or MW for the trained group's untrained leg, E_{PRE} refers to mean PRE-training PT or MW for the trained group's untrained leg; C_{POST} refers to mean POST-training PT or MW for the controls' untrained leg while C_{PRE} refers to the mean PRE-training PT or MW for the control group's untrained leg.

3.3.6 Statistical analysis

Statistical analysis was performed using SPSS software for Windows, version 18.0 (SPSS Inc, Chicago, IL - USA). Unless otherwise stated, all values are reported as means ± standard deviation (SD). An *a priori* power analysis assuming an expected effect size (Cohen's *d*) of 0.55 and a statistical power of 0.80 at an alpha level of 0.05, was performed to detect the appropriate sample size which resulted in a number of 15 subjects per group.

Demographic variables were analyzed at baseline with Student t-test or Chi-Square test, when appropriate. Homogeneity of variances between groups for dynamometric variables was evaluated by Levene's test.

The intra-machine and measurements' validity and reliability were assessed employing a two-way random single measures intra-class correlation coefficient ($ICC_{2,1}$). The intraclass correlation coefficients (ICC) were calculated taking a value <0.4 as an index of poor reliability, 0.4 to 0.75 fair to good reliability, and >0.75 excellent reliability [24].

PT, MW and MW/PT from 30 subjects were analyzed using a repeated measures analysis of variance (ANOVA) using GROUP (CT, Control) and TIME (PRE, POST) as factors. When significance was achieved, pairwise comparisons with Bonferroni adjustment were used. If significant, main effects or interactions were detected, simple main effects analysis followed using one-way ANOVA or dependent *t*-tests when appropriate. Paired *t* tests were employed to evaluate any difference in measurements of muscle performance variables both at 90 and 45°/s of angular velocity.

Cohen's *d* effect size magnitudes (small≤0.5; moderate 0.51-0.79; large≥0.8) were also used to quantify differences in the data after intervention.

Pearson's correlation analysis was used for linear correlation between PT and MW at the two velocities.

3.4 Results

The primary analysis involved all thirty subjects. At baseline, CT (*n*=15) and Control (*n*=15) groups were statistically homogeneous for gender, age and weight (Table 1). All subjects proved to be right-footed at the lower limb dominance tests and the dominant limb was always found to be the strongest, with no statistical difference in dynamometric parameters between groups.

ICC values, indicating trial-to-trial reliability of PT and MW measurements, ranged from 0.93 to 0.98 at 90°/s and 45°/s.

3.4.1 Cross-Training of muscle performance by PT

A significant main effect of TIME was detected for both the untrained (90°/s: $F_{1,27}=13.66$; $p=0.001$; 45°/s: $F_{1,27}=22.96$; $p<0.0005$) and the trained limb (90°/s: $F_{1,27}=27.87$; $p<0.0005$; 45°/s: $F_{1,27}=27.18$; $p=0.0005$). A TIME*GROUP interaction effect was observed for the untrained (90°/s: $F_{1,27}=14.82$; $p=0.0002$; 45°/s: $F_{1,27}=18.61$; $p<0.0005$) as well as the trained leg (90°/s: $F_{1,27}=9.06$; $p<0.006$; 45°/s: $F_{1,27}=28.93$; $p<0.0005$).

When comparing PRE-POST *within-subjects*, the CT group showed a significant strength increase in the untrained limb at both angular velocities, namely a CT-effect, which is shown in Figure 1 and reported in Table 2. Only the CT group exhibited a significant increase in PT which was detected in both the untrained (Table 2: 90°/s: $p=0.009$; $d=0.92$; 45°/s: $p<0.001$; $d=1.02$) and trained (Table 3: 90°/s: $p=0.0006$; $d=1.07$; 45°/s: $p<0.001$; $d=1.29$) sides.

After training, the *between-subjects* analysis revealed a significant difference between groups for both the untrained (90°/s: $F_{1,28}=6.02$; $p=0.02$; 45°/s: $F_{1,28}=26.99$; $p=0.01$) and trained side (90°/s: $F_{1,28}=8.09$; $p=0.008$; 45°/s: $F_{1,28}=11.99$; $p=0.002$). Net PT gains from baseline in the untrained and trained limb are shown in Figure 2 and reported in Table 2 and Table 3, respectively. A significantly greater increase at 90°/s than 45°/s ($p=0.003$) was detected in the untrained limb while no significant difference by angular velocity ($p=0.16$) was observed in the trained limb.

3.4.2 Cross-Training of muscle performance by MW

A significant main effect of TIME was detected for the untrained (90°/s: $F_{1,26}=19.04$; $p<0.0005$; 45°/s: $F_{1,26}=17.54$; $p<0.0005$) as well as the trained leg (90°/s: $F_{1,26}=13.92$; $p<0.0005$; 45°/s: $F_{1,26}=21.06$; $p<0.0005$). A TIME*GROUP interaction effect was observed for both the untrained ($F_{1,26}$=10.36; $p<0.004$; 45°/s: $F_{1,26}$=11.31; $p<0.0005$) and the trained leg (90°/s: $F_{1,26}$=10.31; $p<0.006$; 45°/s: $F_{1,26}$=9.41; $p<0.005$).

After training, the *within-subjects* gains in MW of the untrained limb were significant only in the CT group at both angular velocities, as shown in Figure 2 and reported in Table 2. Compared to baseline, the CT group showed a significant increase in MW in the untrained (90°/s: p=0.005; d=1.08; 45°/s: $p<0.0005$; d=1.34) as well as in the trained (90°/s: $p<0.0005$; d=1.76; 45°/s: $p<0.0005$; d=1.3) sides.

The *between-subjects* analysis revealed a significant difference between groups for the untrained (90°/s: $F_{1,28}$=7.81; p=0.01; 45°/s: $F_{1,28}$=8.4; p=0.009) and trained sides (90°/s: $F_{1,28}$=18.54; $p<0.0005$; 45°/s: $F_{1,28}$=7.52; $p<0.01$). Net MW gains from baseline by side and by angular velocity are shown in Figure 2. Net MW gains from baseline in the untrained and trained limb are shown in Figure 3 and reported in Table 2 and Table 3, respectively. A significantly greater increase at 45°/s than 90°/s (p=0.002)was detected in the untrained limb while no significant difference by angular velocity (p=0.08) was observed in the trained limb.

3.4.3 Work-to-peak torque relationship

Percent net changes in MW occurred to a greater extent than PT at 45°/s (p=0.04), while no significant difference (p=0.11) was detected at 90°/s (Table 2).

The relationship between MW and PT, expressed as MW/PT ratio, increased from PRE- to POST only in the CT group, in both sides and at the two angular velocities, with the exception of the untrained side at 90°/s (Table 4).

At both angular velocities, MW and PT were significantly correlated (Pearson's r coefficients: 0.57-0.85 at 90°/s and 0.77-0.88 at 45°/s; all $p<0.0001$) in both groups.

3.5 Discussion

This is the first report showing in a *between-subjects* design a contralateral transfer of maximal strength and maximal work in AD muscles after unilateral training. A transfer asymmetry was observed, with a greater improvement in muscle performance of the untrained leg than of the trained one. Finally, changes in the proportion of PT and MW contribution to muscle performance were also evidenced.

3.5.1 The Cross-Training effect in ankle dorsiflexors

This study showed that after a 4-week period of unilateral training of AD, the contralateral untrained muscles exhibited a significant increase of performance at both 90 and 45°/s, ranging 18-27% for PT and 29-37% for MW, with high effect sizes (Cohen's d >0.9). This extent of crossed transfer in PT far exceeds the 1.5-8.4% increases reported by the few CT-studies conducted on AD muscles in healthy subjects [14-16] and is similar to the 31% shown in stroke patients [17]. Such studies used intervention protocols other than ours, like an 8-week mixed isokinetic training [15] or a six-week isometric training [16,17].

A main issue of CT studies is reporting *within-subjects* rather than *between-subjects* results [2,4]. The present study was carried out according to a *between-subjects* design, therefore muscle performance of the untrained legs was compared between trained and untrained subjects. This allowed controlling and estimating the familiarization/learning-effect, which is highly associated with strength testing procedures [4] and has been pointed out as a serious concern, since muscle testing itself can improve performance due to habituation of subjects to the test procedure [25]. In this study we observed a familiarization/learning-effect that, depending on angular velocities, was 0.2-2.1% in PT and 9.8-11% in MW. The magnitude of the contralateral net gain (PT: 17.9-27.5%;

MW: 29.6-37%) that we found in the AD was greater than that reported in similar *between-subjects* studies performed on wrist extensor muscles (maximal isometric strength: 7%) [26] and consistent with that reported in untrained thigh muscles (PT: 35%) [27]. However, given the atypical physiological and biomechanical properties of AD muscles [28], generalizing these findings to other muscle groups should be done cautiously.

Interestingly, when comparing PRE-POST gains in muscle performance by side, data showed a greater increase in the untrained limb compared to the trained one. This led to an unexpected significant decrease of the stronger limb's superiority over the weaker in generating work, reducing the physiological strength asymmetry detectable between sides in healthy subjects. Such finding is surprising since it is generally accepted that the gain of strength in the untrained limb is a 25-50% fraction of that in the trained one [1,2]. Similar findings were reported in previous studies performed in the upper limbs, where the preferential direction from dominant to non-dominant side has been accounted for the transfer-effect [29]. The preferential dominant to non-dominant direction criterion might not apply to lower limbs where limb dominance is highly debated and still controversial. In fact, the dominance in lower limbs is not as obvious as handedness and should be viewed in the perspective of the different roles of the two legs, one involved in mobility and the other in stability [30]. Our apparently striking results can be better explained by the maximal-intensity exercise here employed which has been reported to improve economy, rate of force development and maximal strength more than conventional submaximal strength training regimens [31]. Furthermore, maximal-intensity exercise has been proved to highly impact on neural factors underpinning strength adaptations to high-intensity training in both the trained [22,23] and untrained limb in absence of muscle mass increase [32].

3.5.2 Relationship between peak torque and maximal work

We comprehensively assessed muscle performance not only by PT, which represents maximal muscle capability at one point but also by MW that indicates the capability to maintain strength over distance and over time. Our findings showed for the first time a significantly greater transfer of MW than PT, according to the limb dominance. This suggests that reporting both PT and MW can be useful when describing muscle performance and its training-induced changes. However, basing on high correlation coefficients, previous studies stated interchangeability between these parameters, acknowledging PT as the only necessary measure in isokinetic testing [8,12-13]. Conversely, other studies showed that high correlations alone do not justify the interchangeable use of these parameters, concluding that PT and MW are not interchangeable [9,33]. In our study these measures improved differently after training, depending on the angular velocity, with MW increasing more than PT at 45°/s, which may prove clinically relevant in those conditions where choosing the proper training velocity is crucial. These findings are consistent with the idea that PT and MW are complementary rather than interchangeable [9,33]. Accordingly, despite high correlations that we also observed, PRE-POST changes in MW/PT ratio suggest that these parameters contribute with different proportions to muscle performance of the AD after training at different velocities. MW/PT ratio, which describes the mutual relationship between these parameters, may represent a novel index in the interpretation of isokinetic data, after opportune validation.

3.6 Conclusions

The different velocity-dependent response of PT and MW to training indicates that work assessment can complement the conventional peak torque analysis. Furthermore, the MW/PT ratio may help to discriminate the relative contributions of these parameters to muscle performance, at baseline and after training.

The comprehensive assessment of PT and MW may unveil the full potential of the CT in rehabilitative settings. In particular, the occurrence of the CT-effect in AD, with a greater gain in the untrained than trained muscles, has interesting practical implications especially in clinical conditions characterized by a predominantly unilateral hyposthenia, which makes the weaker limb difficult or impossible to train.

3.7 Table And Figure

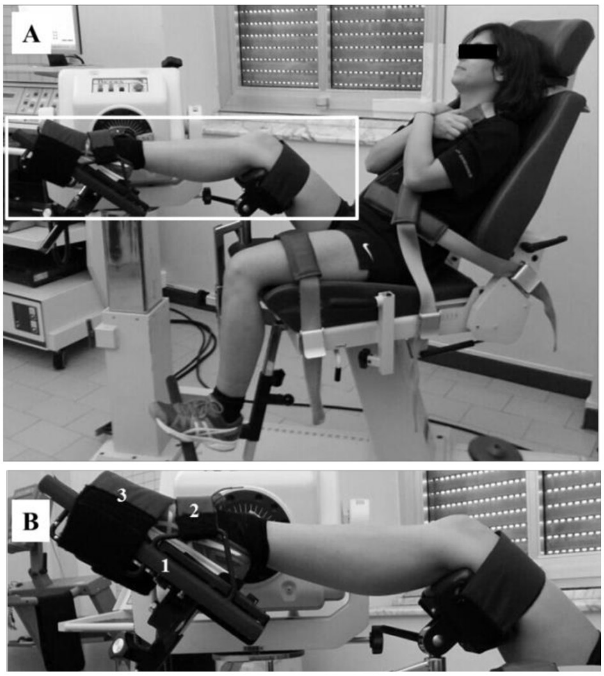


Figure 1 Experimental set-up used for testing and training (A). The subject was positioned in the modified seated position according to Backman and Oberg [19]. Inset (B) shows details of the positioning. 1=foot platform; 2=proximal strap; 3=distal strap.

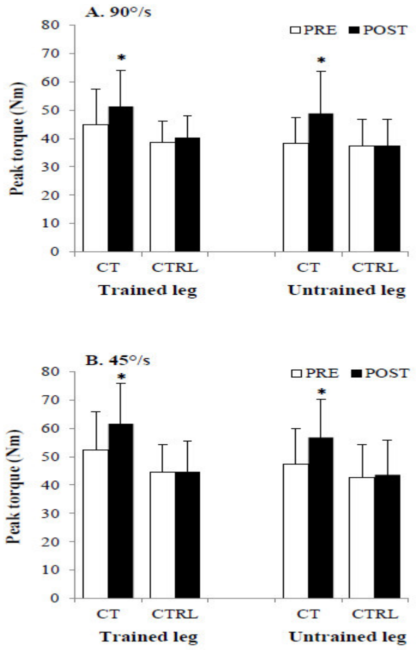


Fig. 2 Average peak torque (±SD) values for the cross-training (CT) and control (CTRL) groups at baseline (PRE) and after the 4-week training or no-intervention period (POST), respectively. Data are shown for the stronger trained and weaker untrained legs and by isokinetic angular velocity (**A**: 90°/s; **B**: 45°/s); * denotes a significant change (*p*<0.005) from PRE to POST.

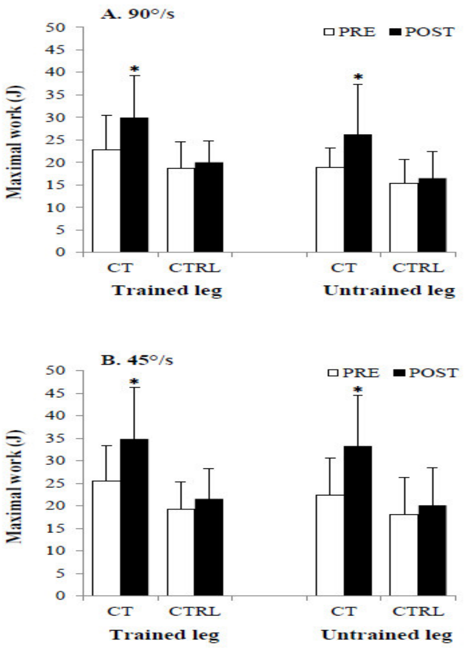


Fig. 3 Average maximal work (±SD) values for the cross-training (CT) and control (CTRL) groups at baseline (PRE) and after the 4-week training or no-intervention period (POST), respectively. Data are shown for the stronger trained and weaker untrained legs and by isokinetic angular velocity (**A**: 90°/s; **B**: 45°/s); * denotes a significant change ($p<0.005$) from PRE to POST.

Table 1. Demographic characteristics of the participants.

	CT (n = 15)	CONTROL (n = 15)	Statistics
Age (years) *95% CI*	25.7 ± 5.4 *22.7 – 28.7*	27.7 ± 3.7 *25.6 – 29.7*	$F_{1,29}$ = 1.42; $p = 0.24$
Gender (%)	F: 5 (33.3%) M: 10 (66.7%)	F: 4 (36.4%) M: 11 (63.6%)	Pearson's $\chi 2$: $p = 0.5$
Weight (kg) *95% CI*	67.1 ± 13.0 *59.9 – 74.3*	73.9 ± 10.2 *68.3 – 79.5*	$F_{1,29}$ = 2.58; $p = 0.12$

CT = Cross-Training group; CI = Confidence Interval; F = Females; M = Males

Table 2. PRE to POST changes in muscle performance of the untrained ankle dorsiflexion muscles *within-* and *between-subjects*.

Dynamo-metric variables	CT			CONTROLS			CT *vs* CONTROLS
	PRE	POST	PRE-POST *Vithin-subjects*	PRE	POST	PRE-POST *Within-subject.*	PRE-POST *Between-subjec*
PT 90°/s	38.3 ±7.5	48.9 ±14.9	+27.7%**	37.4±9.5	37.5±9.3	+0.2%	+27.5%*
95% CI	*(34.2 – 42.4)*	*(40.6 – 57.2)*		*(28.1 – 42.7)*	*(32.1 – 42.9)*		
PT 45°/s	47.3±12.5	56.8±13.5	+20.0%**	42.7±11.7	43.6±12.3	+2.1%	+17.9%*
95% CI	*(40.4 – 54.2)*	*(49.3 – 64.3)*		*(36.2 – 49.3)*	*(36.8 – 50.4)*		
MW 90°/s	18.8±4.4	26.2±11.1	+39.4%**	15.3±5.4	16.8±5.4	+9.8%	+29.6%*
95% CI	*(16.4 – 21.2)*	*(20.1 – 32.3)*		*(12.3 – 18.3)*	*(13.8 – 19.8)*		
MW 45°/s	22.5±8.1	33.3±11.2	+48.0%***	18.1±8.3	20.1±8.3	+11.0%	+37.0%**
95% CI	*(18.0 – 28.0)*	*(27.1 – 39.5)*		*(13.1 – 21.1)*	*(13.0 – 26.8)*		

CT = Cross-Training group; PT = Peak Torque; MW = Maximal Work; 90°/s and 45°/s = values of isokinetic angular velocities; CI = Confidence Intervals. Contralateral net transfer *between-subjects* calculated by Carroll's equation (Carroll et al. 2006).

*Significant for p<0.05; ** Significant for p<0.01; *** Significant for p<0.0005

Table 3. PRE to POST changes in muscle performance of the trained ankle dorsiflexion muscles *within-* and *between-subjects*.

Dynamo-metric variables	CT			CONTROLS			CT *vs* CONTROLS
	PRE	POST	PRE-POST *Within-subjects*	PRE	POST	PRE-POST *Within-subjects*	PRE-POST *Between-subject*
PT 90°/s	44.9±12.5	51.3±12.7	+14.2%**	38.7±7.4	40.3±7.8	+4.1%	+10.1%**
95% CI	*(38.0 - 51.8)*	*(44.3 - 58.3)*		*(34.6 - 42.8)*	*(35.8 - 44.8)*		
PT 45°/s	52.5±13.8	62.2±15.5	+18.5%**	44.4±9.7	44.6±10.8	+0.4%	+18.1%**
95% CI	*(45.6 - 60.1)*	*(53.7 - 70.8)*		*(39.1 - 49.8)*	*(38.4 - 50.8)*		
MW 90°/s	22.7±7.7	29.9±9.3	+31.7%***	18.6±6.0	20.0±4.7	+7.5%	+24.2%***
95% CI	*(18.4 – 26.9)*	*(24.8 - 35.0)*		*(15.3 - 21.9)*	*(17.3 - 22.7)*		
MW 45°/s	25.5±7.8	33.7±10.9	+32.1%***	21.6±6.0	21.8±5.8	+0.9%	+31.2%**
95% CI	*(21.2 - 29.8)*	*(27.7 - 39.7)*		*(17.3 - 26.8)*	*(18.5 - 26.1)*		

CT = Cross-Training group; PT = Peak Torque; MW = Maximal Work; 90°/s and 45°/s = values of isokinetic angular velocities; CI = Confidence Intervals. Contralateral net transfer *between-subjects* calculated by Carroll's equation (Carroll et al. 2006).

*Significant for p<0.05; ** Significant for p<0.01; *** Significant for p<0.0005

Table 4. PRE to POST changes in Work-to-Peak torque ratio.

ANGULAR VELOCITY	LIMB*	GROUP	MW/PT PRE	MW/PT POST	*p* value
90°/s	Dominant	CT	0.52	0.59	0.04
		Control	0.41	0.43	0.35
	Non-dominant	CT	0.49	0.54	0.09
		Control	0.41	0.44	0.58
45°/s	Dominant	CT	0.49	0.57	<0.0005
		Control	0.44	0.48	0.29
	Non-dominant	CT	0.47	0.59	<0.0005
		Control	0.44	0.46	0.80

CT = Cross-Training; MW = maximal work; PT = peak torque; *dominant (stronger) = trained limb in CT and untrained limb in Control; non-dominant (weaker) = untrained limb in both CT and Control groups.

3.8 References

1. Zhou S. Chronic neural adaptations to unilateral exercise: Mechanisms of cross education. Exerc Sport Sci Rev. 2000;28(4):177-84.
2. Munn J, Herbert RD, Gandevia SC. Contralateral effects of unilateral resistance training: A meta-analysis. J Appl Physiol. 2004;96(5):1861-6.
3. Hortobágyi T, Scott K, Lambert J, Hamilton G, Tracy J. Cross-education of muscle strength is greater with stimulated than voluntary contractions. Motor Control. 1999;3(2):205-19.
4. Carroll TJ, Herbert RD, Munn J, Lee M, Gandevia SC. Contralateral effects of unilateral strength training: Evidence and possible mechanisms. J Appl Physiol. 2006;101(5):1514-22.
5. Hortobágyi T. Cross education and the human central nervous system. IEEE Eng Med Biol Mag. 2005;24(1):22-8.
6. Fimland MS, Helgerud J, Solstad GM, Iversen VM, Leivseth G, Hoff J. Neural adaptations underlying cross-education after unilateral strength training. Eur J Appl Physiol. 2009;107(6):723-30.
7. Kidgell DJ, Stokes MA, Pearce AJ. Strength training of one limb increases corticomotor excitability projecting to the contralateral homologous limb. Motor Control. 2011;15(2):247-66.
8. Morrissey MC. The relationship between peak torque and work of the quadriceps and hamstrings after meniscectomy. J Orthop Sports Phys Ther. 1987;8(8):405-8.
9. Dvir Z, David G. Average or peak moment: Which of the two is more suitable to represent isokinetic muscle strength? Isokinetics Exerc Sci. 1995;5(2):93-7.
10. Davies, GJ. A Compendium of Isokinetics in Clinical Usage and Rehabilitation Techniques. 4th Ed. Onalaska, WI: S. & S Publishers; 1992.
11. Kannus P. Isokinetic evaluation of muscular performance: Implications for muscle testing and rehabilitation. Int J Sports Med. 1994;15(SUPPL. 1):S11-8.

12. Woodson C, Bandy WD, Curis D, Baldwin D. Relationship of isokinetic peak torque with work and power for ankle plantar flexion and dorsiflexion. J Orthop Sports Phys Ther. 1995;22(3):113-5.
13. Bandy WD, Timm KE. Relationship between peak torque, work, and power for knee flexion and extension in clients with grade I medial compartment sprains of the knee. J Orthop Sports Phys Ther. 1992;16(6):288-92.
14. Tachino K, Susaki T, Yamazaki T. Effect of electro-motor stimulation on the power production of a maximally stretched muscle. Scand J Rehabil Med. 1989;21(3):147-50.
15. Uh B, Beynnon BD, Helie BV, Alosa DM, Renstrom PA. The benefit of a single-leg strength training program for the muscles around the untrained ankle: A prospective, randomized, controlled study. Am J Sports Med. 2000;28(4):568-73.
16. Dragert K, Zehr EP. Bilateral neuromuscular plasticity from unilateral training of the ankle dorsiflexors. Exp Brain Res. 2011;208(2):217-27.
17. Dragert K, Zehr EP. High-intensity unilateral dorsiflexor resistance training results in bilateral neuromuscular plasticity after stroke. Exp Brain Res. 2013;225(1):93-104.
18. Urbaniak, GC and Plous S (2013) Research Randomizer (Version 4.0); from http://www.randomizer.org/
19. Backman E, Oberg B. Isokinetic muscle torque in the dorsiflexors of the ankle in children 6-15 years of age. Normal values and evaluation of the method. Scand J Rehabil Med. 1989;21(2):97-103.
20. Hoffman M, Schrader J, Applegate T, Koceja D. Unilateral postural control of the functionally dominant and nondominant extremities of healthy subjects. J Athl Train. 1998;33(4):319-22.
21. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev. 2001;81(4):1725-89.
22. Moritani T, DeVries HA. Neural factors versus hypertrophy in the time course of muscle strength gain. Am J Phys Med. 1979;58(3):115-30.

23. Sale DG. Neural adaptation to resistance training. Med Sci Sports Exerc. 1988;20(5 SUPPL.):S135-45.
24. Shrout PE, Fleiss JL. Intraclass correlation: uses in assessing rater reliability. Psychol Bull. 1979; 86(2):430-428.
25. Gleeson NP, Mercer TH. The utility of isokinetic dynamometry in the assessment of human muscle function. Sports Med. 1996;21(1):18-34.
26. Lee M, Gandevia SC, Carroll TJ. Short-term strength training does not change cortical voluntary activation. Med Sci Sports Exerc. 2009 Jul;41(7):1452-60.
27. Goodwill AM, Pearce AJ, Kidgell DJ. Corticomotor plasticity following unilateral strength training. Muscle and Nerve. 2012;46(3):384-93.
28. Tallent J, Goodall S, Hortobágyi T, St Clair Gibson A, Howatson G. Corticospinal responses of resistance-trained and un-trained males during dynamic muscle contractions. J Electromyogr Kinesiol. 2013;23(5):1075-81.
29. Farthing JP, Borowsky R, Chilibeck PD, Binsted G, Sarty GE. Neuro-physiological adaptations associated with cross-education of strength. Brain Topogr. 2007;20(2):77-88.
30. Gentry V, Gabbard C. Foot-preference behavior: a developmental perspective. J Gen Psychol. 1995;122(1):37-45.
31. Heggelund J, Fimland MS, Helgerud J, Hoff J. Maximal strength training improves work economy, rate of force development and maximal strength more than conventional strength training. Eur J Appl Physiol. 2013;113(6):1565-1573.
32. Enoka RM. Neural adaptations with chronic physical activity. J Biomech. 1997;30(5):447-455.
33. Kramer JF, MacDermid J. Isokinetic measures during concentric-eccentric cycles of the knee extensors. Aust J Physiother. 1989;35(1):9-14.

Study 4: Isokinetic cross-training effect in foot drop following common peroneal nerve injury

4.1 Abstract

Background: To our knowledge, no studies on foot drop (FD) caused by peripheral nerve lesion investigated whether unilateral training of the unaffected ankle dorsiflexors induces a worthy strength improvement in the affected-untrained leg, namely a cross-training (CT) effect.

Objective: Testing for the first time cross-training in FD following peripheral nerve injury.

Methods: A 59-year-old man, who suffered in childhood from surgical-induced damage of the common peroneal nerve, performed an 8-week maximal-intensity isokinetic training of the healthy leg. Before and after training, subject underwent: 1) bilateral isokinetic dynamometry to measure peak torque, maximal and total work; 2) functional and mobility tests: 6-minute walking test, 10-meter walking test, timed-up-and-go test and ankle range-of-motion (ROM); 3) neurophysiological recordings: motor thresholds, cortical silent period of the hemisphere innervating the affected tibialis anterior, mean EMG recruitment.

Results: After cross-training, the affected-untrained dorsiflexors showed notable increases in muscle performance for all the dynamometric parameters. Similarly, all functional tests, included the ankle dorsiflexion active ROM considerably improved. Cortical silent period was reduced and maximal EMG recruitment increased.

Conclusions: Maximal isokinetic cross-training induced improvements in the affected-untrained leg performance associated to a parallel increase in cortico-spinal drive. In this report cross-training was a viable rehabilitative approach to FD.

4.2 Background

The Cross-Training (CT) effect is the improvement of strength in one limb, following unilateral training of the contralateral homologous muscles, underpinned by multiple-level neural adaptations. The reported magnitude of the strength transfer is 5-25%, which has potential clinical implications in pathological asymmetric conditions.[1] Extensively investigated in orthopaedic patients with an immobilized limb, CT has been recently tested in post-stroke hyposthenia of ankle dorsiflexors.[2] The term foot drop (FD) commonly refers to a weakness or contracture of the ankle joint muscles, arising from several diseases involving the central and/or the peripheral nervous system.[3] To our knowledge no data are currently available regarding the employment of CT in the management of FD due to peripheral nerve damage. The present work tested the effects of unilateral training of the unaffected leg on the performance of the affected ankle dorsiflexor muscles as well as functional and neural changes in an inveterate case of FD.

4.3 Methods

4.3.1 Case Description

A 59-year-old man suffered, at the age of 11, FD from iatrogenic damage of the left common peroneal nerve following partial fibulectomy for osteomyelitis. At 5-year follow-up, the patient underwent the transfer of the tibialis posterior tendon which was re-routed through the interosseus membrane to the tibialis anterior (TA) and peroneus brevis tendons[4] with poor clinical results. To improve impaired gait and social participation, the subject underwent periodical cycles of conventional physiotherapy mainly consisting of electrical muscle stimulation and direct strength-training of the affected ankle dorsiflexors. While fairly coping with such inveterate disability, the subject got notice of our CT research protocols (ClinicalTrials.gov Identifier: NCT02010398) and volunteered for this study after signing an informed consent form. All study procedures were approved by the local Ethical Committee (Bioethics Board of ASL n.1-Sassari, prot. 1160/L, June 28, 2013).

4.3.2 Intervention

The intervention consisted of a 8-week maximal-intensity isokinetic training (32 sessions) of the unaffected ankle dorsiflexors, with 3 sets of 6 repetition-maximum (RM) at 90°/s of angular velocity and 3 sets of 4 RM at 45°/s, with a 2-minute rest in between. Prior to the intervention, the subject was instructed to "push hard and fast as you can" with the trained leg, while keeping the contralateral one relaxed.

4.3.3 Assessment procedures

All examinations were performed before, after 4 and 8 weeks of CT by the same operator at the same time of the day. During the testing, any subject-operator interaction was accurately avoided. Muscle performance of the ankle dorsiflexors was bilaterally assessed on an isokinetic dynamometer (Biodex System-3PRO) with the subject seated with hip at 90°, knee at 30° and ankle in full plantar flexion, taken as starting position. Extraneous body movements were minimized by restraining shoulders, hips, thighs and ankles through straps and belts. In a separate session, the subject was familiarized with the isokinetic testing to minimize the potential effects of learning associated to testing procedures.[5] Before the test, the patient underwent a predefined 5-minute warm-up consisting of 2 sets of 4 to 6 submaximal repetitions at each angular velocity. Peak torque (PT) and maximal work (MW) were bilaterally recorded at 90°/s /s and 45°; total work (TW) was measured during a 30-repetition bout at 180°/s, to assess endurance. Functional performance was assessed by the 6-Minute Walking Test (6MWT), 10-Meter Walking Test (10MWT) and the Timed-Up-and-Go test (TUG). The active and passive range-of-motion (ROM) of the ankle joint were also measured.

Surface EMG was recorded from the affected TA, amplified (Digitimer D360 amplifier), filtered (3 Hz–6 kHz) and sampled (15 kHz) with a 1401plus A/D converter (CED) and Signal 5.0 software. Mean EMG activity was assessed during five maximal voluntary contractions. Excitability of the cortical motor area innervating the affected-untrained TA was probed using transcranial magnetic stimulation (Magstim 200) to measure resting (RMT) and active (AMT) motor thresholds and duration of the cortical silent period (cSP), at intensities of 120% and 150% of RMT.

4.4 Results

In comparison to baseline, a 4-week isokinetic CT period was able to induce, in the affected-untrained leg, a remarkable improvement of all dynamometric parameters (with the exception of PT at 90°/s) and functional outcomes. After further 4 weeks of CT, muscular and functional performance levelled to a plateau, while PT at 90°/s increased and TW further improved. Neurophysiological recordings from the affected TA showed a progressive increase of the mean EMG recruitment and a parallel decrease of cSP duration, with no changes in RMT and AMT. Dynamometric, functional and neurophysiological parameters recorded from the affected-untrained limb are reported in Table 1.

4.5 Discussion

This is the first report of the occurrence of the CT effect in a case of a typical FD caused by peripheral nerve lesion. This case is paradigmatic since the subject up to that time received all standard approaches employed in the management of inveterate FD, including surgery, ankle-foot orthoses and conventional physiotherapy.[3] A maximal-intensity isokinetic training of the contralateral healthy leg induced a considerable increase in the performance of the untrained-affected ankle dorsiflexors in terms of maximal strength, maximal work and total work. Muscle performance gains were associated to functional improvements of walking, mobility and active ROM of the ankle joint. These data are consistent with previous studies reporting the CT phenomenon in ankle dorsiflexors of both healthy subjects[6] and stroke patients.[2]

After cross-training, an increase in the EMG recruitment and a parallel decrease in the duration of the cSP were observed in the affected-untrained TA. These findings suggest that an enhancement of the cortico-spinal drive to the affected-untrained ankle dorsiflexors may contribute to the CT-induced improvement of muscle performance and functional outcomes, in line with other reports in healthy subjects.[7]

Appropriate assessment and intervention procedures were used in this study. In fact, isokinetic dynamometry is widely acknowledged as a valid and reliable testing tool in patients with neuromuscular diseases, providing accurate and reproducible values.[8] Moreover, neurophysiological recordings of cortico-spinal excitability have been shown as consistent and highly repeatable, also in ankle dorsiflexors.[8]

In conclusion, this case report provides a preliminary evidence for the CT as a viable and promising rehabilitative approach to FD. Neurophysiological data additionally suggest that neural adaptations are concomitant with motor recovery, even after long time from the occurrence of the nervous damage.

4.6 Table And Figure

Table 1 – Dynamometric, functional and neurophysiological raw measures obtained from the untrained-affected ankle dorsiflexors* before, after 4 weeks and 8 weeks of maximal-intensity isokinetic Cross-Training.

	Parameters		**Before CT**	**4-week CT**	**8-week CT**	**Maximal change from baseline**
Dynamometric	PT 90°/s (Nm)		18 [32]	18 [33]	22 [38]	+22%
	PT 45°/s (Nm)		23 [39]	31 [51]	31 [53]	+34%
	MW 90°/s (J)		3 [13]	6 [17]	6 [19]	+100%
	MW 45°/s (J)		11 [22]	20 [33]	20 [36]	+81%
	TW180°/s (J)		15 [138]	34 [192]	51 [238]	+240%
Functional	Passive ROM (degr)		14	14	14	-
	Active ROM (degr)		4	11	12	+200%
	6MWT (m)		390	410	425	+9%
	10 MWT	(sec)	7.4±0.2	6.9±0.1	7.0±0.4	-6%
		(m/s)	1.35	1.45	1.43	+6%
	TUG (sec)		6.8±0.3	6.0±0.5	6.1±0.2	-11%
Neurophysiological	Mean EMG (μV)		180	250	330	+83%
	RMT (%MSO)		48	49	48	-
	AMT (%MSO)		37	37	36	-
	cSP 120% RMT (ms)		154	144	136	-11%
	cSP 150%RMT (ms)		196	182	176	-10%

*Numbers in brackets refer to dynamometric measures performed in the trained healthy leg.

CT = Cross-Training; PT = Peak Torque; MW = Maximal Work; TW = Total Work; 90°/s, 45°/s and 180°/s = values of angular velocities; ROM = Range of Motion; 6MWT = six minutes walking test; 10 MWT = ten meters walking test; TUG = Time-up-and-go test; 10MWT and TUG are expressed as mean ± standard deviation obtained by averaging four repeated measures; EMG = mean value of EMG activity recorded during five maximal voluntary contractions lasting one second; RMT = Resting Motor Threshold; AMT = Active Motor Threshold; %MSO = % of Maximal Stimulator Output; cSP = cortical Silent Period; 120%RMT and 150%RMT = intensity of transcranial magnetic stimulation. Maximal changes from baseline: + = increase; - = decrease.

4.7 References

1. Zhou S. Chronic neural adaptations to unilateral exercise: mechanisms of cross education. Exerc. Sport Sci. Rev. 2005; 28(4): 177-184.
2. Dragert K, Zehr EP. High-intensity unilateral dorsiflexor resistance training results in bilateral neuromuscular plasticity after stroke. Exp Brain Res. 2013; 225(1): 93-104.
3. Sackley C, Disler PB, Turner-Stokes L, Wade DT, Brittle N, Hoppitt T. Rehabilitation interventions for foot drop in neuromuscular disease. Cochrane Database Syst Rev. 2009; Jul 8(3): CD003908
4. Shah RK. Tibialis posterior transfer by interosseous route for the correction of foot drop in leprosy. Int Orthop. 2009; 33(6): 1637-1640.
5. Carroll TJ, Herbert RD, Munn J, Lee M, Gandevia SC. Contralateral effects of unilateral strength training: evidence and possible mechanisms. J Appl Physiol. 2006; 101(5): 1514-1522.
6. Dragert K, Zehr EP. Bilateral neuromuscular plasticity from unilateral training of the ankle dorsiflexors. Exp Brain Res. 2011; 208(2): 217-227.
7. Latella C, Kidgell DJ, Pearce AJ. Reduction in corticospinal inhibition in the trained and untrained limb following unilateral leg strength training. Eur J Appl Physiol. 2012: 112(8): 3097-3107.
8. Tallent J, Goodall S, Hortobágyi T, St Clair Gibson A, French DN, Howatson G. Repeatability of corticospinal and spinal measures during lengthening and shortening contractions in the human tibialis anterior muscle. PLoS ONE. 2012; 7(4): e35930. doi: 10.1371/journal.pone.0035930. Epub 2012 Apr 26.

Study 5: Reproducibility and responsiveness of strength measurements in patients with multiple sclerosis

5.1 Abstract

Background: In patients with multiple sclerosis (PwMS) the assessment of strength impairment and interpretation of changes induced by training is challenging. This study comprehensively investigated the reproducibility and responsiveness of strength measurements in ankle dorsiflexion muscles (DF) of PwMS.

Methods: Cross-sectional study for adults with relapsing remittent multiple sclerosis (MS). The primary outcomes were peak moment (PM) and maximal work (maxW). Twenty PwMS were tested isokinetically at baseline, after one day and after one week. Outcome measures were analyzed using repeated-measures ANOVA, effect size (ES), intraclass correlation coefficients (ICC), standard error of measurement (SEM), coefficient of variation (CV) and the smallest real difference (SRDi).

Findings: PM and maxW proved highly reproducible (ICCs>0.9) and precise among the 3 testing sessions (SEM=±0.31-0.83; CV=3.3-14.6%). The mean SRD values for clinically meaningful changes ranged 11-13% for PM and 14-20% for maxW.

Interpretation: Inter-session reproducibility of PM and maxW, obtained isokinetically in DF, is excellent in PwMS. Moreover, SRD provides guidance for interpreting strength measures and defining clinically meaningful changes if an intervention is to be introduced.

5.2 Introduction

Reproducibility and responsiveness are two closely related methodological properties of clinical measurements.[1] Reproducibility, which is also known as test-retest reliability, is defined as the ability to measure attributes in a consistent manner when administered on several occasions.[1] Responsiveness is the ability to detect relevant changes over time[2] or, in clinical settings, changes in unstable subjects.[1] Despite their crucial role in research as well as in clinical and sports scenarios, quantification and interpretation of both reproducibility and responsiveness is often unclear or poorly addressed.[3]

This is of particular concern in rehabilitation, where one of the primary reasons for repeatedly assessing patients is to determine the effects of non-invasive interventions on specific outcome parameters (OPs).[4] Moreover, a large part of these OPs are performance-based, spanning a large range of human abilities from segmental movement patterns to cognitive abilities while requiring full patient collaboration. Therefore, findings derived from repeated measurements are susceptible to several sources of error, including inconsistencies caused by the subject/patient, the test procedure, the instrument, the test environment and the examiner.[5] Furthermore, the measurement error may not be negligible when fluctuating physical OPs such as muscle strength and endurance are under evaluation. Inevitably, if improperly assessed or inadequately verified, both the baseline levels and change scores attributed to an intervention and relating to a given OP may lead to misinterpretation. Thus, the detailed evaluation of reproducibility and responsiveness is essential in order to establish consistent and effective tools for clinical applications as well as for research.

These considerations are particularly pertinent in the case of patients with multiple sclerosis (PwMS) who present with overall deconditioning characterized by reduced muscle strength and increased fatigability. Rice et al. (1992) reported that in PwMS maximum voluntary strength was 30–70% lower than controls.[6] The decreased ability of PwMS to fully activate muscles contributes to the physical deconditioning commonly observed in MS.[7,8] This feature has been linked to decreased muscle cross-sectional area, reduced aerobic-oxidative energy supply,[9] increased muscular fatigue,[10] decreased motoneuron firing rates[6] and reduced cortico-spinal neural drive.[11]

Regarding quantitative assessment of muscle performance, measurement of maximal voluntary strength requires the subject to fully activate muscles. However, since this ability is impaired in MS,[7,8] patients may experience day-to-day fluctuations in the degree of strength or fatigue,[12] which translate into high test-retest variability in the related physical OPs.[13] The extent to which these fluctuations could affect the reproducibility of muscular strength measurements in PwMS has been the topic of only a handful of studies which reported excellent test-retest reproducibility, particularly in knee flexors and extensors' strength.[4,7,12,14] However, all of these studies related to two time points (test and retest) only, although the inclusion of a third time point may portray reproducibility in a more clinically meaningful way.[15] Moreover, while none of these studies looked into the issue of responsiveness, reproducibility was expressed in terms of intraclass correlation coefficients (ICC) which are known to be insensitive to changes that occur within a group in a uniform mode.[16] Significantly, the error of measurement has not been specifically assessed in the abovementioned studies and therefore determination of cut-off values for clinically meaningful change, could not be derived.

These voids have motivated the present study in which the reproducibility and responsiveness of strength measurements in PwMS at 3 different time points was undertaken. Maximal strength was assessed dynamometrically with respect to the ankle dorsiflexors (DF) and expressed in terms of both the peak moment (PM) and the maximal work (maxW). These OPs provide somewhat different but complementary points of view regarding muscle function, as indicated in recent studies on these muscles at baseline and after a training period.[17,18] This study focused on the DF as the model muscle group since they are commonly impaired in patients with neurological disorders[19] while the expected day-to-day variability in strength of PwMS poses a specific clinical challenge.

5.3 Methods

5.3.1 Participants

The design of the study was set as cross-sectional. Twenty PwMS were recruited from those taking part in a larger interventional trial taking place in the facilities of the University Hospital of Sassari from July 2013 to May 2015 (ClinicalTrials.gov identifier: NCT02010398). To highlight any difference by side in the measurements' reproducibility, PwMS with a predominantly unilateral hyposthenia of the DF were selected. Inclusion criteria were: diagnosis of relapsing-remittent MS (according to 2010 revision of diagnostic criteria[20]); patient-reported evidence of strength asymmetry between DF muscles; age ≥18 years; independent deambulation with or without unilateral assistance; Expanded Disability Status Scale (EDSS) score ≤6.5 with Pyramidal Functional System score ≥3. Exclusion criteria were: any medical condition contra-indicating participation in strength testing exercises; occurrence of relapses, treatment with corticosteroid and/or botulinum toxin, variations in Disease-Modifying Drugs or symptomatic treatment in the previous 6 months; severe ataxia and postural instability; major depression; clinically relevant cognitive deficits; participation in rehabilitative or training programs within 6 months prior to the study. Patients deemed eligible after clinical examination were asked to refrain from any other exercise activity during the study.

The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional Bioethics Committee of the Local Health Authority (ASL n.1-Sassari, Italy; Prot. number 1160/L/2013). A written informed consent was obtained by all the participants before enrollment.

5.3.2 Muscle Strength Testing

Muscle performance of the DF was assessed on both legs with an isokinetic dynamometer (Biodex System 3, Biodex Medical Systems, Shirley, NY, USA). The test was conducted in sitting position with the knee flexed at 30° and the ankle in full plantar flexion taken as starting position.[21] Subjects were firmly stabilized at the dynamometer using straps. Participants had no prior experience of performance testing with dynamometers. In the 2 weeks preceding the criterion test all participants attended a familiarization session with the isokinetic strength testing protocol to minimize the potential effects of practice-based improvement associated with this procedure.[22]

All subjects underwent a predefined 5-minute warm-up/familiarization by performing one set of 2-to-4 submaximal repetitions at angular velocities of 10°/s and 45°/s with a 3-minute rest in between. Following a 5-min rest, the criterion test consisted of 2 repetitions at 10°/s and 4 repetitions at 45°/s. These velocities were chosen in view of the difficulties experienced by neurological patients in achieving high angular velocities.[23] The less-affected leg (LA) was tested first. A 6-min rest elapsed between the testing of the LA and the more-affected leg (MA). The entire procedure was repeated in 3 different sessions: 1) criterion test (baseline); 2) 1 day retest (1-day reproducibility) and 3) 1-week retest (1-week reproducibility).

5.3.3 Data analysis

Statistical analysis was performed using the SPSS software for Windows, version 18.0 (SPSS Inc, Chicago, IL - USA). Means, standard deviations (SD) and 95% confidence intervals (CI) were calculated by side (MA and LA) and by angular velocity (10 and 45°/s) for each OP: the PM (in Nm) and the maxW (in J) across the 3 testing sessions. Each OP was determined as the maximum value recorded among the tests. The equality of variances was assessed by Levene's test. Gender differences in baseline strength of DF muscles were preliminarily analyzed by independent *t*-tests. Since no significant differences emerged, data from male and female patients were pooled.

A repeated-measures analysis of variance (ANOVA) was conducted to compare measurements among the sessions. Significance was set at $p<0.05$ and when detected, pairwise comparisons with Bonferroni adjustment were performed to locate differences.

Cohen's *d* effect size magnitudes (small≤0.5; moderate 0.51-0.79; large≥0.8) were also used to estimate the clinical relevance of the inter-session differences.[24] Test-retest reproducibility and responsiveness were estimated by calculating four different numerical indices: 1) *Intraclass correlation coefficient* (ICC), which is generally accepted as the preferred method of quantifying relative reproducibility, using a 2-way random $ICC_{2,1}$ for single measures;[2,25] 2) S*tandard error of measurement* (SEM), which quantifies the precision of individual scores on a test and provides an absolute index of reproducibility.[26] The SEM was calculated as follows: SEM= SD x √(1-ICC); $SEM_{\%}$= (SEM/mean) x 100; 3) *Coefficient of variation* (CV), which is an index of absolute reproducibility and is employed to interpret the consistency of measurements across time. It was calculated as a percentage: CV%= (method error/mean)*100, where method error= $SD_{diff}/\sqrt{2}$;[27] 4) *Smallest real difference* (SRD), which is a measure of responsiveness and is defined as the smallest change in score that exceeds the error of measurement and may thus be recognized as clinically meaningful at the level of the individual patient.[27] The individual SRD (SRDi) was calculated according to the following formula: SRDi = 2.77 x SEM and reported also as SRDi% calculated by 2.77 x (mean SEM/grand mean OP) x 100, where grand mean represents the mean of the three testing sessions.

5.4 Results

All individuals completed the 3 testing sessions. All tests were well tolerated by the patients and no exacerbation occurred throughout the entire duration of the study.

Demographic and clinical characteristics of the twenty PwMS are detailed in Table 1. The participants exhibited a clear strength asymmetry with MA being significantly weaker than LA both in terms of PM and maxW (all *p* values ≤0.0005). When comparing PM- and maxW-based asymmetries, the latter was significantly greater (Table 2).

5.4.1 Difference by means

Means, standard deviations, confidence intervals and main effects for the isokinetic findings of DF strength are presented in Table 3 for the two OPs (PM and maxW), the side (LA and MA) and the angular velocity (10 and 45°/s). Levene's test for equality of variances revealed the homoscedastic nature of all OPs. Regarding LA, the repeated-measures ANOVA revealed a main effect of time. Bonferroni-adjusted pairwise comparisons detected significant reductions in both PM and maxW between sessions 1 and 3 (except for maxW at 10°/s). The parallel analysis for MA indicated a main time effect with significant differences not only between Session 1 and 3 but also between Session 1 and 2 (with the exception of maxW at 45°/s). For both limbs and angular velocities, the effect sizes calculated between sessions 1 vs. 2 and 1 vs. 3 were small for PM and maxW, ranging 0.1 to 0.4.

5.4.2 Reproducibility and responsiveness

Absolute and relative reproducibility and responsiveness of the strength measurements are presented in Table 4. The ICCs of PM and maxW are detailed for relative reproducibility purposes by limb (LA and MA), angular velocity (10 and 45°/s) and type of comparison (Session 1 vs. 2; Session 1 vs. 3; Session 1 vs. 2 vs. 3). Overall, in both legs and at both angular velocities, all ICCs were ≥ 0.9 while the CV ranged 3.3-14.6%, with a mean value of 8.2%. All SEM values, irrespective of the unit of measurement (Nm or J), ranged 0.32-0.83 while absolute SRDi values ranged: 1.25-3.31. SRDi% values of the OPs are outlined in Table 4.

5.5 Discussion

The present study comprehensively investigated the reproducibility and responsiveness of maximal strength measurements in the ankle DF of PwMS presenting with predominantly unilateral hyposthenia. Notably, when quantifying strength deficits by side, the asymmetry between the LA and MA limbs appeared better portrayed by maxW (20-24%) than PM (12-14%). A magnitude of asymmetry greater than 20% is generally considered to be pathological.[28] This may have practical implications since deficits in strength but also intervention-induced changes are commonly quantified in terms of PM.[29] In this context, when isokinetic dynamometry is the tool of choice, maxW should complement PM in the interpretation of isokinetic findings, adding valuable information for the assessment of muscle performance in PwMS.[17,18]

5.5.1 Reproducibility

Relative reproducibility, estimated by ICCs and by the associated 95% Cis, proved excellent for PM and maxW, for both limbs and angular velocities. This general finding supports previous research relating to the ability of isokinetic dynamometry to yield clinically acceptable consistency of strength measurements in PwMS under dynamic[12] and isometric conditions.[4,7,14] However, the present study focused on dynamic DF strength, rather than its static counterpart,[7] the former serving an important function in ambulation. Moreover, since previous studies related mainly to knee muscles, a direct comparison is difficult. In line with the acknowledged consistency of isokinetic dynamometry,[30] the present data indicate a low variability of measurements over time. Regarding absolute reproducibility, low CV and SEM scores further confirmed that the variability observed among tests was not due to a real difference in strength. The inclusion of 3 rather than 2 testing sessions and of a dedicated familiarization procedure may have contributed to attenuate errors of measurements.

Notably, in this study the reproducibility of both PM and maxW proved excellent. While a similar result has already been established for PM,[29] no previous reference could be traced for maxW. This is an interesting finding since, although complementary,[17,18] PM and maxW provide quite different information on muscle performance: while PM is an instantaneous measure of force exerted at one single point, maxW is the average measure of the torque output throughout the entire range of motion.[31]

Regardless of the excellent reproducibility observed across the 3 testing sessions both at the relative and absolute level, significant mean variations of strength outcomes were detected. This finding supports previous arguments on the day-to-day strength variability in PwMS.[12] However, despite being statistically significant over time, such differences should be considered functionally unremarkable and clinically not relevant considering the trivial effect size detected between sessions.

Weir (2005) suggested that large ICCs (indicating good reproducibility) and significant trials effect were not necessarily mutually exclusive.[32] For an ANOVA to be significant, the mean differences between trials must be large, whereas the error term must be small, the latter taking place when all subjects behave similarly across testing sessions.[32] The present findings pointing to excellent ICCs alongside significant but clinically irrelevant differences between sessions, raise concerns on the exclusive employment of relative reproducibility regardless of hypothesis tests for bias, effect size and measures of absolute reproducibility such as CV and SEM.

Since isokinetic dynamometers provide highly reproducible measurements, the pathophysiological and clinical features of MS might have played a role in the observed variability of the OPs. In particular, neuromuscular recruitment is impaired in PwMS who exhibit a day-to-day variability which may affect the levels of muscle performance.[7,12] Compared to normative values of maximal strength measured in healthy subjects under isokinetic conditions,[17,18,33] participants in this study exhibited lower levels of muscle performance. However, different age, testing positions and angular velocities make the present strength measures difficult to compare to these reports.

In the present cohort characterized by a marked DF strength asymmetry, the MA showed a greater variability in strength than LA. This finding is likely to support a direct relationship between the degree of muscle weakness and the day-to-day variability in muscle performance shown by PwMS.

5.5.2 Responsiveness

Measurement error not only affects a single measurement but also a consecutive series of measurements aimed to reflect change, namely responsiveness. The SRD, which is a responsiveness parameter, determines whether a true change rather than a measurement error has occurred over time. Based on the results of the present study, any change in muscle performance falling below the individual cut-off value calculated by SRDi should be discarded even if statistically significant since it can be attributed to the measurement noise. This concept is particularly meaningful if an intervention is then introduced, since not every difference carries a clinical meaning.[34] In this perspective, no efforts should be spared in establishing a reliable and valid baseline while minimizing the measurement error which is crucial to detect true changes from random findings following a therapeutic intervention, particularly in “unstable” individuals such as PwMS.

5.6 Conclusions

Although muscle performance in MS is generally considered highly variable over time, in our sample of patients with a predominantly unilateral hyposthenia of DF, measurements of maximal strength in terms of both PM and maxW, showed excellent reproducibility in the less and in the more compromised limb.

Appropriate procedures are advisable in PwMS when assessing physical capacities and/or the occurrence of meaningful changes that may be induced by conservative interventions. These procedures should include methodological steps such as the inclusion of a proper familiarization protocol and the provision of at least 3 testing sessions or adding tests until a plateau in performance occurs. Moreover, statistical analysis should be employed to establish relative and absolute reproducibility of the measuring devices and of the OPs. Finally, incorporating SRD for responsiveness along with repeated-measures ANOVA may help optimize the quantification and interpretation of test-retest results, which is particularly challenging in PwMS.

The current findings of this study set for the first time a realistic target for judging success (improvement) in muscle strength in PwMS due to pharmacological or exercise intervention. However, these findings should be cautiously generalized to muscle groups other than the ankle DF considering the neurophysiological and biomechanical peculiarities of these muscles.[35] Therefore further research is needed to examine reliability, reproducibility and responsiveness of strength measurements in a greater sample and in more conventionally investigated body territories

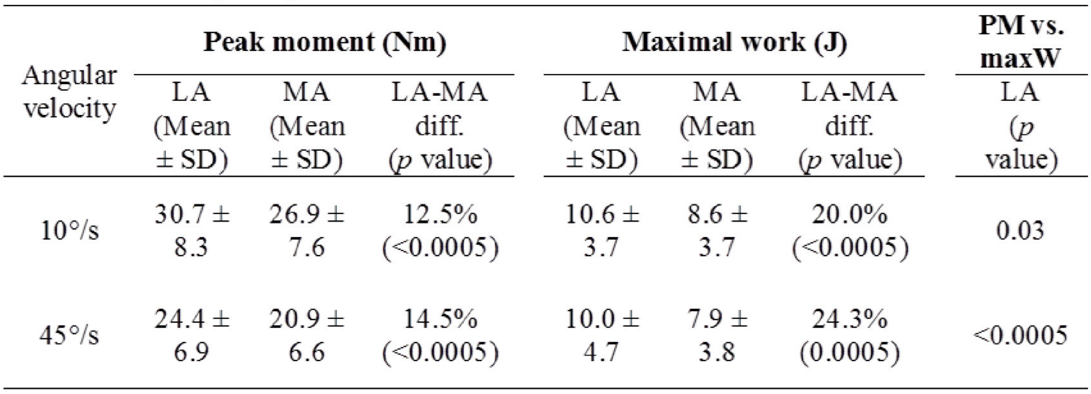
5.7 Table And Figure

Table 1. Demographic and clinical features of participants.

PwMS	Mean	SD
Gender (M:F)	4:16	-
Age (years)	44	11.2
Weight (kg)	60.2	13.4
Height (cm)	163	0.1
BMI (kg/m^2)	22.4	4.3
Disease duration (years)	14.4	8.4
EDSS*	3	1.9-4.1

PwMS, patients with multiple sclerosis; SD, Standard Deviation; M, males; F, females; BMI, Body Mass Index; EDSS, Expanded Disability Status Scale; *score calculated by median and interquartile range.

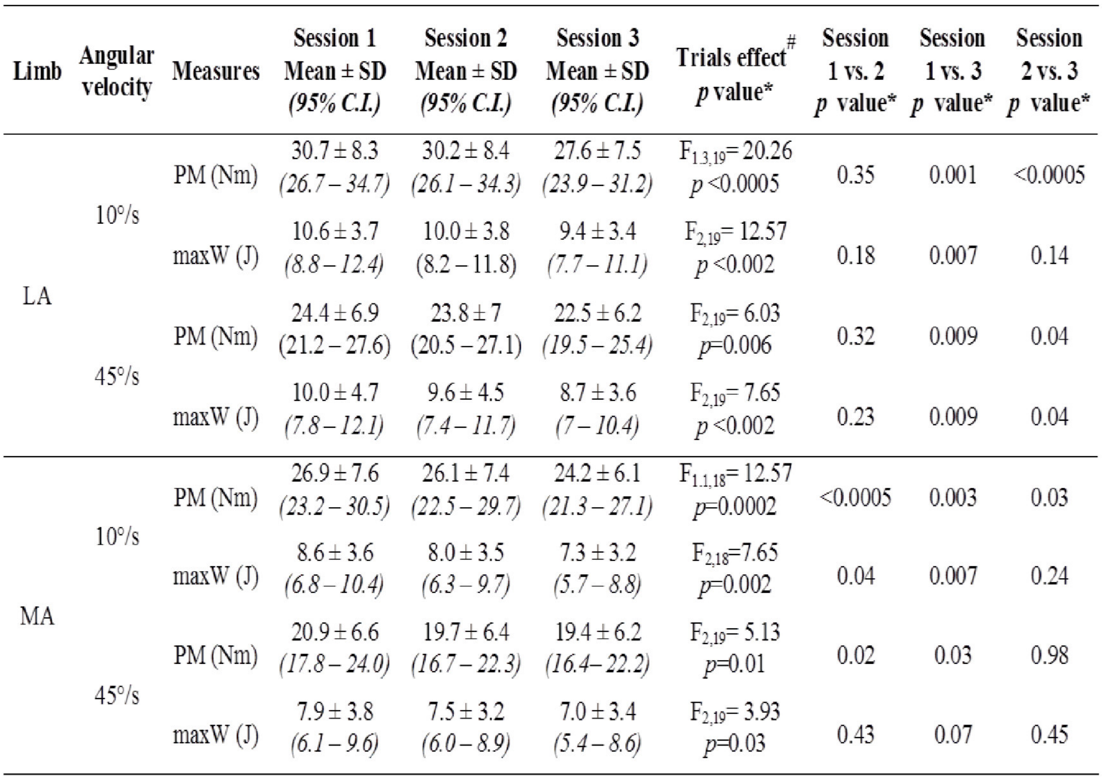
Table 2. Dynamometric features of ankle dorsiflexion muscles in the less- and more-affected limb of participants.



Angular velocity	Peak moment (Nm)			Maximal work (J)			PM vs. maxW
	LA (Mean ± SD)	MA (Mean ± SD)	LA-MA diff. (*p* value)	LA (Mean ± SD)	MA (Mean ± SD)	LA-MA diff. (*p* value)	LA (*p* value)
10°/s	30.7 ± 8.3	26.9 ± 7.6	12.5% (<0.0005)	10.6 ± 3.7	8.6 ± 3.7	20.0% (<0.0005)	0.03
45°/s	24.4 ± 6.9	20.9 ± 6.6	14.5% (<0.0005)	10.0 ± 4.7	7.9 ± 3.8	24.3% (0.0005)	<0.0005

PM, Peak Moment; maxW, maximal Work; Nm, Newton metre; J, Joule; 10°/s and 45°/s, degrees of isokinetic angular velocities; LA, Less-affected limb; MA, Most-affected limb; LA-MA diff, strength asymmetry between LA and MA expressed as percent difference; SD, Standard Deviation; *p value calculated by paired t-tests.

Table 3. Descriptive statistics of the less-affected and most-affected ankle dorsiflexion muscles.



Limb	Angular velocity	Measures	Session 1 Mean ± SD *(95% C.I.)*	Session 2 Mean ± SD *(95% C.I.)*	Session 3 Mean ± SD *(95% C.I.)*	Trials effect# *p* value*	Session 1 vs. 2 *p* value*	Session 1 vs. 3 *p* value*	Session 2 vs. 3 *p* value*
LA	10°/s	PM (Nm)	30.7 ± 8.3 *(26.7 – 34.7)*	30.2 ± 8.4 *(26.1 – 34.3)*	27.6 ± 7.5 *(23.9 – 31.2)*	$F_{1.3,19}$= 20.26 p <0.0005	0.35	0.001	<0.0005
		maxW (J)	10.6 ± 3.7 *(8.8 – 12.4)*	10.0 ± 3.8 (8.2 – 11.8)	9.4 ± 3.4 *(7.7 – 11.1)*	$F_{2,19}$= 12.57 p <0.002	0.18	0.007	0.14
	45°/s	PM (Nm)	24.4 ± 6.9 (21.2 – 27.6)	23.8 ± 7 (20.5 – 27.1)	22.5 ± 6.2 *(19.5 – 25.4)*	$F_{2,19}$= 6.03 p=0.006	0.32	0.009	0.04
		maxW (J)	10.0 ± 4.7 *(7.8 – 12.1)*	9.6 ± 4.5 *(7.4 – 11.7)*	8.7 ± 3.6 *(7 – 10.4)*	$F_{2,19}$= 7.65 p <0.002	0.23	0.009	0.04
MA	10°/s	PM (Nm)	26.9 ± 7.6 *(23.2 – 30.5)*	26.1 ± 7.4 *(22.5 – 29.7)*	24.2 ± 6.1 *(21.3 – 27.1)*	$F_{1.1,18}$= 12.57 p=0.0002	<0.0005	0.003	0.03
		maxW (J)	8.6 ± 3.6 *(6.8 – 10.4)*	8.0 ± 3.5 *(6.3 – 9.7)*	7.3 ± 3.2 *(5.7 – 8.8)*	$F_{2,18}$=7.65 p=0.002	0.04	0.007	0.24
	45°/s	PM (Nm)	20.9 ± 6.6 *(17.8 – 24.0)*	19.7 ± 6.4 *(16.7 – 22.3)*	19.4 ± 6.2 *(16.4– 22.2)*	$F_{2,19}$= 5.13 p=0.01	0.02	0.03	0.98
		maxW (J)	7.9 ± 3.8 *(6.1 – 9.6)*	7.5 ± 3.2 *(6.0 – 8.9)*	7.0 ± 3.4 *(5.4 – 8.6)*	$F_{2,19}$= 3.93 p=0.03	0.43	0.07	0.45

LA, Less-affected limb; MA, Most-affected limb; PM, Peak Moment; maxW, maximal Work; Nm, Newton metre; J, Joule; 10°/s and 45°/s, degrees of isokinetic angular velocities; SD, Standard Deviation; C.I., Confidence Interval; #Trials effect indicating the main effect of time across the 3 testing sessions and calculated by repeated measures ANOVA; **p* value calculated by Bonferroni-adjusted pairwise comparisons.

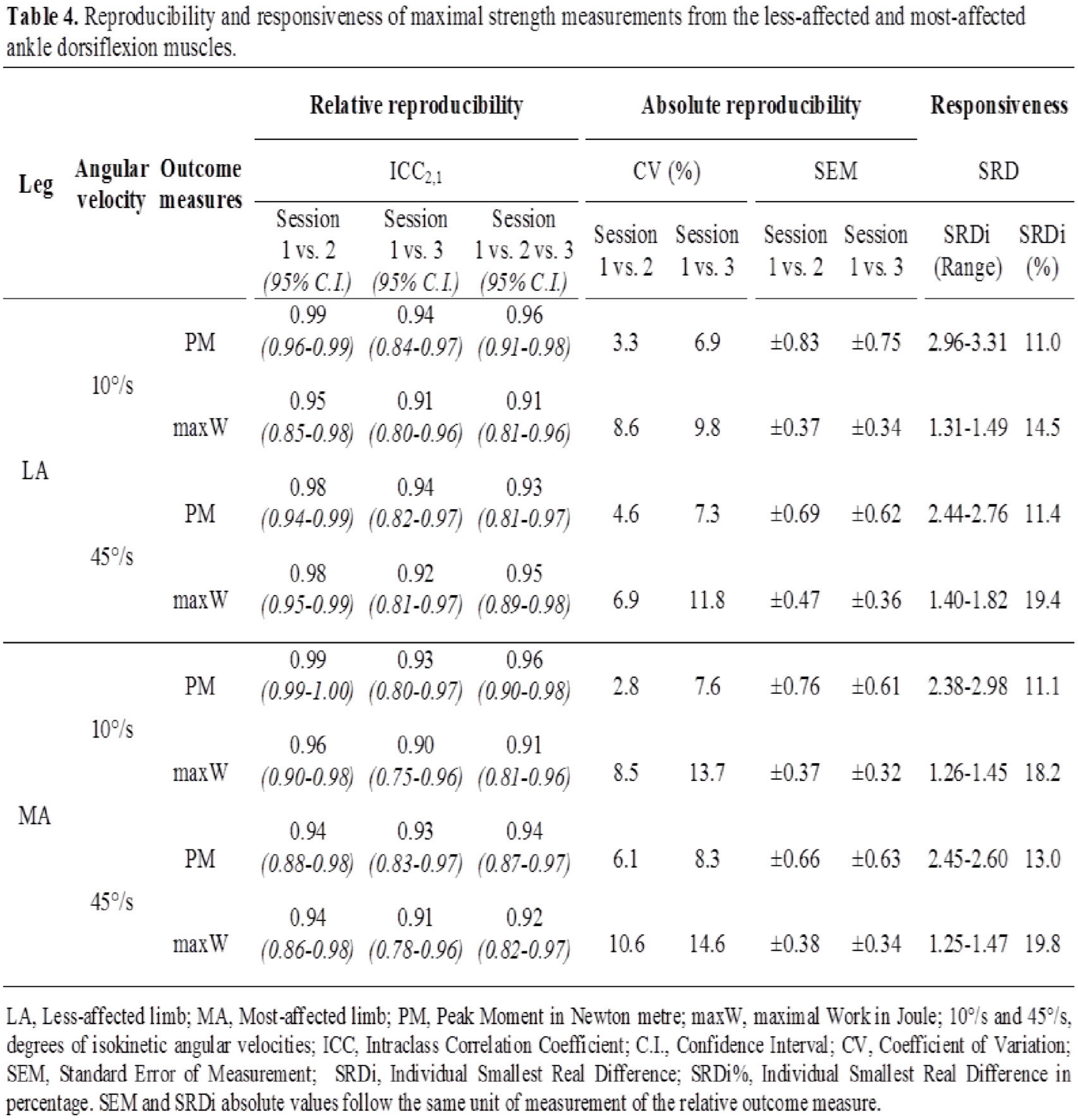


Table 4. Reproducibility and responsiveness of maximal strength measurements from the less-affected and most-affected ankle dorsiflexion muscles.

Leg	Angular velocity	Outcome measures	Relative reproducibility			Absolute reproducibility				Responsiveness	
			$ICC_{2,1}$			CV (%)		SEM		SRD	
			Session 1 vs. 2 *(95% C.I.)*	Session 1 vs. 3 *(95% C.I.)*	Session 1 vs. 2 vs. 3 *(95% C.I.)*	Session 1 vs. 2	Session 1 vs. 3	Session 1 vs. 2	Session 1 vs. 3	SRDi (Range)	SRDi (%)
LA	10°/s	PM	0.99 *(0.96-0.99)*	0.94 *(0.84-0.97)*	0.96 *(0.91-0.98)*	3.3	6.9	±0.83	±0.75	2.96-3.31	11.0
		maxW	0.95 *(0.85-0.98)*	0.91 *(0.80-0.96)*	0.91 *(0.81-0.96)*	8.6	9.8	±0.37	±0.34	1.31-1.49	14.5
	45°/s	PM	0.98 *(0.94-0.99)*	0.94 *(0.82-0.97)*	0.93 *(0.81-0.97)*	4.6	7.3	±0.69	±0.62	2.44-2.76	11.4
		maxW	0.98 *(0.95-0.99)*	0.92 *(0.81-0.97)*	0.95 *(0.89-0.98)*	6.9	11.8	±0.47	±0.36	1.40-1.82	19.4
MA	10°/s	PM	0.99 *(0.99-1.00)*	0.93 *(0.80-0.97)*	0.96 *(0.90-0.98)*	2.8	7.6	±0.76	±0.61	2.38-2.98	11.1
		maxW	0.96 *(0.90-0.98)*	0.90 *(0.75-0.96)*	0.91 *(0.81-0.96)*	8.5	13.7	±0.37	±0.32	1.26-1.45	18.2
	45°/s	PM	0.94 *(0.88-0.98)*	0.93 *(0.83-0.97)*	0.94 *(0.87-0.97)*	6.1	8.3	±0.66	±0.63	2.45-2.60	13.0
		maxW	0.94 *(0.86-0.98)*	0.91 *(0.78-0.96)*	0.92 *(0.82-0.97)*	10.6	14.6	±0.38	±0.34	1.25-1.47	19.8

LA, Less-affected limb; MA, Most-affected limb; PM, Peak Moment in Newton metre; maxW, maximal Work in Joule; 10°/s and 45°/s, degrees of isokinetic angular velocities; ICC, Intraclass Correlation Coefficient; C.I., Confidence Interval; CV, Coefficient of Variation; SEM, Standard Error of Measurement; SRDi, Individual Smallest Real Difference; SRDi%, Individual Smallest Real Difference in percentage. SEM and SRDi absolute values follow the same unit of measurement of the relative outcome measure.

5.8 References

1. Beckerman H, Roebroeck ME, Lankhorst GJ, Becher JG, Bezemer PD, Verbeek AL. Smallest real difference, a link between reproducibility and responsiveness. *Qual Life Res.* 2001;10(7):571-578.
2. Guyatt G, Walter S, Norman G. Measuring change over time: assessing the usefulness of evaluative instruments. *J Chronic Dis.* 1987;40(2):171-178.
3. Streiner DL. Learning how to differ: agreement and reliability statistics in psychiatry. *Can J Psychiatry.* 1995 Mar;40(2):60-66.
4. Paltamaa J, West H, Sarasoja T, Wikström J, Mälkiä E. Reliability of physical functioning measures in ambulatory subjects with MS. *Physiother Res Int.* 2005;10(2):93-109. Erratum in: *Physiother Res Int.* 2006;11(2):123.
5. Thomas JR, Nelson JK. Research methods in physical activity. Champagne, IL: Human Kinetics Books, 1990.
6. Rice CL, Vollmer TL, Bigland-Ritchie B. Neuromuscular responses of patients with multiple sclerosis. *Muscle Nerve.* 1992;15(10):1123-1132.
7. Schwid SR, Thornton CA, Pandya S, Manzur KL, Sanjak M, Petrie MD, McDermott MP, Goodman AD. Quantitative assessment of motor fatigue and strength in MS. *Neurology.* 1999;11;53(4):743-750.
8. Kjølhede T, Vissing K, Dalgas U. Multiple sclerosis and progressive resistance training: a systematic review. *Mult Scler.* 2012 Sep;18(9):1215-1228.
9. Kent-Braun JA, Ng AV, Castro M, et al. Strength, skeletal muscle composition, and enzyme activity in multiple sclerosis. *J Appl Physiol.* 1997;83:1998-2004.
10. Lenman AJ, Tulley FM, Vrbova G, Dimitrijevic MR, Towle JA. Muscle fatigue in some neurological disorders. *Muscle Nerve.* 1989;12(11):938-942.
11. Fimland MS, Helgerud J, Gruber M, Leivseth G, Hoff J. Enhanced neural drive after maximal strength training in multiple sclerosis patients. *Eur J Appl Physiol.* 2010;110(2):435-443.

12. Lambert CP, Archer RL, Evans WJ. Muscle strength and fatigue during isokinetic exercise in individuals with multiple sclerosis. *Med Sci Sports Exerc.* 2001;33(10):1613-1619.
13. Sandroff BM, Sosnoff JJ, Motl RW. Physical fitness, walking performance and gait in multiple sclerosis. *J Neurol Sci.* 2013;15;328(1-2):70-76.
14. Bever CT, Anderson PA, Smith GV, Panitch HS, Johnson KP. Isometric Measurement of Hamstrings and Quadriceps Strength in Multiple Sclerosis Patients: Sensitivity and Variability. *Neurorehabil Neural Repair.* 1995;9(4): 221-227.
15. Wu X, Hart CH, Draper TW, Olsen JA. Peer and teacher sociometrics for preschool children: cross-informant concordance, temporal stability and reliability. Merrill-Palmer Quarterly 2001;47(3).416-443.
16. Portney LG, Watkins MP. Foundations of Clinical Research: Applications to Practice (3rd Edition), 2008.
17. Manca A, Solinas G, Dragone D and Deriu F. Isokinetic testing of muscle performance: new concepts for strength assessment. *Isokinet Exerc Sci* 2015*a*;DOI 10.3233/IES-15-566.
18. Manca A, Solinas G, Dragone D, Dvir Z, Deriu F. Characterization of ankle dorsiflexors performance in healthy subjects following maximal-intensity isokinetic resistance training. *J Electromyogr Kinesiol.* Epub ahead of print 17 Jun 2015. doi: 10.1016/ j.jelekin.2015.06.002.
19. Sackley C, Disler PB, Turner-Stokes L, Wade DT, Brittle N, Hoppitt T. Rehabilitation interventions for foot drop in neuromuscular disease. *Cochrane Database Syst Rev.* 2009 Jul 8;(3):CD003908.
20. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol.* 2011;69(2):292-302.

21. Bäckman E, Oberg B. Isokinetic muscle torque in the dorsiflexors of the ankle in children 6-15 years of age. Normal values and evaluation of the method. *Scand J Rehabil Med.* 1989;21(2):97-103.
22. Carroll TJ, Herbert RD, Munn J, Lee M, Gandevia SC. Contralateral effects of unilateral strength training: evidence and possible mechanisms. *J Appl Physiol (1985).* 2006;101(5):1514-1522.
23. Tiffreau V, Ledoux I, Eymard B, Thévenon A, Hogrel JY. Isokinetic muscle testing for weak patients suffering from neuromuscular disorders: a reliability study. *Neuromuscul Disord.* 2007;17(7):524-531.
24. Cohen, J. Statistical power analysis for the behavioral sciences (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.
25. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull.* 1979;86(2):420-428.
26. Harvill LM. Standard error of measurement. Educ Meas Issues Pract. 1991;10:33-41.
27. Lexell JE, Downham DY. How to assess the reliability of measurements in rehabilitation. *Am J Phys Med Rehabil.* 2005;84(9):719-723.
28. Sapega AA. Muscle performance evaluation in orthopaedic practice. *J Bone Joint Surg Am.* 1990;72(10):1562-1574.
29. Kannus P. Isokinetic evaluation of muscular performance: Implications for muscle testing and rehabilitation. *Int J Sports Med.* 1994; 15(1):11-18.
30. Gleeson NP, Mercer TH. The utility of isokinetic dynamometry in the assessment of human muscle function. *Sports Med.* 1996;21(1):18-34.
31. Morrissey MC. The relationship between peak torque and work of the quadriceps and hamstrings after meniscectomy. *J Orthop Sports Phys Ther.* 1987;8(8):405-408.
32. Weir JP. Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. *J Strength Cond Res.* 2005;19(1):231-240.

33. Harbo T, Brincks J, Andersen H. Maximal isokinetic and isometric muscle strength of major muscle groups related to age, body mass, height, and sex in 178 healthy subjects. *Eur J Appl Physiol.* 2012;112(1):267-275.
34. Dvir Z. Difference, significant difference and clinically meaningful difference: The meaning of change in rehabilitation. *J Exerc Rehabil.* 2015;11(2):67-73.
35. Tallent J, Goodall S, Hortobágyi T, St Clair Gibson A, Howatson G. Corticospinal responses of resistance-trained and un-trained males during dynamic muscle contractions. *J Electromyogr Kinesiol.* 2013 Oct;23(5):1075-1081.

Study 6: Time-course and implications of strength adaptations following high intensity resistance training in patients with multiple sclerosis

6.1 Abstract

Background: No evidence exists regarding the time-course and clinical relevance of muscle strength improvements following resistance training in patients with multiple sclerosis (PwMS).

Objective: The purpose of this study was to investigate the temporal course and the clinical meaningfulness of the changes in strength induced by high-intensity resistance training (HIRT).

Design: Single-group, before-after trial with follow-up.

Setting: Outpatient university hospital.

Patients: Twenty PwMS with predominantly unilateral hyposthenia of the ankle dorsiflexion muscles presenting a mild to moderate didability (EDSS score≤6.5).

Intervention: 6-week maximal concentric isokinetic training of the more affected ankle dorsiflexors. Repeated-measures ANOVA and the individual smallest real difference (SRDi) were employed, respectively, to assess the significance and responsiveness of the training-induced changes in muscle strength after 3 and 6 weeks into training and 12 weeks following its termination.

Measurements: isokinetic peak moment (PM) and maximal work (maxW).

Results: Considerable gains in PM and maxW were already apparent after 3 weeks of HIRT with significant and clinically meaningful improvements which exceeded the respective SRDi cutoff values for meaningful changes. Remarkably, the gains in PM were still maintained at the 12-week follow-up assessment.

Limitations: The primary limitation of this proof-of-concept study is the absence of a control group. Secondly, the present findings in the ankle dorsiflexors should not be generalized to other body districts in consideration of the peculiar features of this muscle group.

Conclusions: Preliminary evidence is provided that a 3-week HIRT induces consistent and meaningful improvements of muscle performance in PwMS. If verified through a properly planned randomized controlle trial, these findings may have practical dose-response and cost-effectiveness implications in the management of muscle weakness in MS.

6.2 Introduction

Muscle weakness is a hallmark symptom reported by people with multiple sclerosis (PwMS) and is associated with reduced functional capacity and increased disability.[1] Along with fatigue it is the most common and disabling symptom in MS.[2] Resistance training (RT) has proven well tolerated by PwMS and capable of improving muscle weakness and self-reported fatigue. The beneficial effects of RT have been shown to translate into increased levels of daily living activities and of the overall quality of life.[2,3]

Different RT protocols are currently employed for improving strength and fatigue in PwMS but no regimen has been portrayed as superior to the others.[4] In a recent systematic review of clinical trials which focused on RT in PwMS,[5] the average duration of the training protocols was 20 weeks (range: 3-104) with a mean frequency of 2.5 sessions per week (range: 2-5) and a total mean of 25 sessions (range: 15-208). Most of the studies that investigated the effects of RT in PwMS reported significant strength improvements in those muscle groups that were specifically targeted during training.[5] The magnitude of improvement observed ranged 7-50%, depending on the type, duration and course of the disease, testing and exercise conditions and the trained muscle group.

However, despite the evidence supporting the beneficial effects of RT on function, mobility and fatigue, the heterogeneity of protocols employed in PwMS raises questions regarding the optimal duration of training and the number of sessions required to elicit significant and meaningful improvements in muscle performance. In particular, the use of high intensity resistance training (HIRT) in PwMS has not been looked at systematically although this topic has received growing attention in recent years, with respect to different patient groups and pathologies.[3,6]

Additionally no specific reference emerges from these studies regarding the limb to be tested and trained,[5] a crucial point in nonsymmetrical weakness where the most compromised of the two limbs might exhibit a different pattern of response to training. Furthermore, assessing muscle strength along the training spectrum rather than only at the beginning and conclusion of training is a significant issue both from the perspectives of both the patient and the clinician.

Therefore, the objective of this exploratory single-group before-after study was to investigate the time-course and clinical relevance of strength adaptations following isokinetic concentric a high-intensity RT (HIRT) of the more affected (MA) ankle dorsiflexion muscles (DFs) in PwMS with predominantly unilateral hyposthenia.

6.3 Methods

6.3.1 Participants

Twenty PwMS (15 females, 5 males; age: 45.0±10.3 years old, weight: 60.8±13.2 kg; body mass index: 22.7±4.2 kg/m^2) referring to our academic hospital participated in this study after signing a written informed consent. A sample of convenience was drawn from an ongoing randomized controlled study from which only subjects undergoing direct training of the weaker limb were selected for the present investigation. Inclusion criteria were: diagnosis of relapsing-remittent MS;[7] patient-reported evidence of strength asymmetry between DF muscles; age≥18 years; independent deambulation with or without unilateral assistance; Expanded Disability Status Scale (EDSS) score≤6.5; Pyramidal Functional System score≥3. Criteria for exclusion or discontinuation were: any contraindication for strength testing exercises; occurrence of relapses, treatment with corticosteroid and/or botulinum toxin, variations in Disease-Modifying Drugs or symptomatic treatment, participation in rehabilitative or training programs in the previous 6 months; severe ataxia, postural instability, major depression, cognitive deficits. Participants were asked to refrain from any other exercise activity during the study. The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Bioethics Committee). Details of data management, monitoring procedures and consent documentation are fully available at the Department of Biomedical Sciences, University of Sassari.

6.3.2 Muscle strength assessment

The strength of the DFs in the MA limb was measured by isokinetic dynamometry (Biodex System 3, Biodex Medical Systems, Shirley, NY, USA). The test was conducted in the sitting position with the trunk inclined at 85°, the knee flexed at 30° and the ankle in full plantar flexion taken as starting position. Subjects were firmly stabilized using straps. The active ankle range of motion (RoM) was measured with an electronic goniometer (Biometrics Ltd., Newport, UK). As all patients were able to dorsiflex the ankle from full plantarflexion to 42-44° of dorsiflexion, the RoM for both the tests and training was adjusted to 40°. Participants were naïve to strength testing with isokinetic dynamometers. In the 2 weeks preceding the criterion test all participants attended a familiarization session with the isokinetic testing protocol to minimize the potential effects of practice-based improvement associated with this procedure.[8] All subjects underwent a 5-minute warm-up by performing one set of 2-to-4 submaximal repetitions at angular velocities of 10°/s and 45°/s with a 3-minute rest in between. Following a 5-min rest, the criterion test consisted of 2 maximum repetitions (RM) at 10°/s and 4 RM at 45°/s, aimed at detecting the highest value for each outcome parameter: the peak moment (PM) and maximal work (maxW). The patient's effort was made only in dorsiflexion while the return motion into full plantarflexion was performed passively by the dynamometer.

To verify the reproducibility of measurements in these patients who are generally considered having high day-to-day variability in strength,[9] the testing procedure was repeated in 3 different sessions before the commencement of the HIRT as follows: criterion test, 1-day retest and 1-week retest. The highest value for each parameter was retained as the baseline level of strength. Once baseline (PRE) was established, the assessment of the DFs strength was carried out 3 weeks after the beginning of the HIRT (INTERMEDIATE), at the end of the 6-week training (POST) and 12 weeks after the completion of HIRT (FOLLOW-UP). The study timeline is summarized in Fig. 1.

Patients with multiple sclerosis underwent a 6-week high intensity resistance training (HIRT) of the more affected ankle dorsiflexion muscles. PRE: baseline assessment with test-retest procedures consisting of 3 isokinetic measurements (test, 1-day and 1-week retests) of maximal strength parameters (peak moment and maximal work at 10 and 45°/s of angular velocity); INTERMEDIATE: assessment performed after 3 weeks of HIRT; POST: assessment performed at the end of the entire training period; FOLLOW-UP: assessment performed 12 weeks after the completion of the training protocol. Arrows with continuous line indicate each HIRT session administered. Arrows with dashed line indicate the assessments performed.

6.3.3 Intervention

Participants underwent a 6-week isokinetic concentric HIRT of the MA DFs, with a frequency of 3 sessions per week on non-consecutive days. After a light warm-up (as described above), subjects performed 3 sets of 4 RM at 45°/s and 3 sets of 4 RM at 10°/s with a 3-min rest given between sets. Each session lasted approximately 25 minutes. During the training, a visual feedback displaying the real-time level of exertion was continuously provided by a monitor. If a session was missed, subjects were allowed to recover it at the end of the cycle to ensure that the minimum target number of 16 sessions was reached.

6.3.4 Data analysis

Statistical analysis was performed using the SPSS software for Windows, version 18.0 (SPSS Inc, Chicago, IL - USA). Power analysis assuming a moderate effect size (Cohen's *d*: 0.7-0.8) and a statistical power of 0.80 at an alpha level of 0.05 revealed a required sample size of 20 subjects. Means, standard deviations (SD) and 95% confidence intervals (CI) were calculated for PM and maxW at the two velocities (10 and 45°/s) at the 4 scheduled time points of assessment.

Equality of variances was assessed by Levene's test while sphericity of data for each variable was verified with the Mauchly's test. When sphericity was violated, the Greenhouse-Geisser correction was applied. Since no significant gender differences in baseline strength emerged, data from males and females were pooled.

Reproducibility of measurements at baseline was estimated by relative (intraclass correlation coefficient analysis, ICC)[10] and absolute indices of reproducibility (coefficient of variation, CV; standard error of measurement, SEM).[11] The smallest real difference for the individual patient (SRDi), which is a measure of responsiveness, was also calculated to determine a cutoff value for detecting clinically meaningful changes over time.[11,12] A difference score (DS) was calculated as the difference between the value in PM or maxW recorded at the intermediate assessment *versus* baseline (3-week DS) as well as that recorded at the POST assessment *versus* baseline (6-week DS). Each DS was calculated individually and was then compared to the absolute SRDi and to the SRDi% score.

To compare measurements among the scheduled time points and highlight any training-induced change a repeated-measures analysis of variance (ANOVA) was conducted along with Bonferroni-adjustment pairwise comparisons with were performed to locate the differences.

Data analyst was blinded to data collection.

6.4 Results

All patients (*n*=20; mean disease duration: 14.9±8.5 years; median EDSS: 3, range: 1.5–6.0) completed the scheduled testing and training sessions with an adherence rate of 16.8±1.1 sessions (93.3%) out of the 18 scheduled. The training regimen was well tolerated by all participants. No harms, relapses or changes in medications occurred during the study. Patients exhibited a clear strength asymmetry in terms of PM and maxW ($p<0.0005$). Compared to normative PM values of the DFs in healthy subjects under similar isokinetic conditions,[13-15] our PwMS exhibited lower levels of muscle performance.

6.4.1 Reproducibility and responsiveness of maximal strength measurements

Absolute and relative reproducibility and responsiveness of the strength measurements obtained from the DFs of the MA limb are presented in Table 1. The ICCs of PM and maxW are outlined with respect to the velocity (10 and 45°/s) and type of comparison (Session 1 vs. 2; Session 1 vs. 3; Session 1 vs. 2 vs. 3). Overall, at both velocities, all ICCs were ≥0.84 while the CV ranged 3.4-15.5%, with a median value of 8.9%. All SEM values, irrespective of the unit of measurement (Nm or J), ranged 0.30-0.89. Absolute SRDi values ranged: 1.16-3.09 while SRDi% scores ranged 10.9-17.7%.

6.4.2 Time course of changes in maximal strength following training

The repeated-measures ANOVA revealed a main effect of time for PM and maxW at both velocities (Table 2). The temporal changes in strength observed at the four assessment points (PRE, INTERMEDIATE, POST and FOLLOW-UP) are displayed in Fig. 2. Bonferroni-adjusted pairwise comparisons showed significant improvements in PM and maxW after 3 weeks of training at both velocities ($p<0.05$) with no further improvement from INTERMEDIATE to POST. However, PM and maxW at POST were significantly higher than baseline both at 10°/s (PM: $p=0.01$; maxW: $p=0.03$) and 45°/s (PM: $p<0.0005$; maxW: $p=0.04$). Significant decreases in strength were observed from POST to FOLLOW-UP at both velocities (PM: $p\leq0.005$; maxW: $p=0.006$) with a return of maxW to pre-training values while PM remained significantly superior to baseline ($p=0.03$).

After the first 3 out of 6 weeks of HIRT, all increases in strength exceeded the SRDi values both in terms of absolute and percent (SRDi%) scores (Table 3). The number of times a patient exceeded the 3-week or 6-week DS was plotted on charts for SRDi and SRDi% (Fig. 3). For both outcome and velocity, at the 3-week assessment more than 50% of the patients exhibited gains in muscle strength which exceeded the SRDi and the SRDi%.

6.5 Discussion

This is possibly the first study describing muscle conditioning in neurological patients where the intervention effect has been assessed both in terms of statistical significance and clinical importance. Furthermore, the temporal efficiency of the intervention was evaluated during the intervention, immediately after its termination and at a 12-week follow-up to render a comprehensive picture of a process intended to strengthen the DFs of the more affected lower extremity in PwMS using isokinetic dynamometry.

The present study demonstrated that in PwMS who trained their weaker DFs intensively for a period of 6 weeks, a considerable part of the total gain in maximal strength was already apparent after 3 weeks with consistent and clinically relevant improvements. It was also concluded that the effect of training on strength largely faded at the follow-up assessment.

First, with respect to the time course of changes in maximal strength following training, previous studies focusing on the effectiveness of RT on muscle weakness in PwMS evaluated muscle performance or physical outcomes only at the beginning and the end of the intervention.[1-3,5,6,16-25] However, no in-depth analysis has hitherto been undertaken with respect to the time-course of these changes. In the present study, strength dynamics was assessed both within the training period and well after its termination. These assessments have revealed that HIRT of the isokinetic concentric type induced a significant increase in maximal strength already after the first 3 weeks of training; extension of the training period by another 3 weeks did not result in further gains although these gains were largely retained. Moreover, judging by the quite stringent standards of SRDi cutoff scores (both absolute and relative) more than 50% of the patients demonstrated an improvement that exceeded the minimal clinically meaningful change. Noteworthy, as this study was based on a relatively small sample size, the cutoffs were both higher than those potentially derived from a larger population. This could result in an even higher proportion of meaningful change as by increasing the sample size the SRDs (both SRDi and SRDi%) could potentially be lower and therefore more patients could cross the cutoff. These findings which corroborate the use of HIRT in PwMS may have practical dose-response and cost-effectiveness implications when defining the training amount to be prescribed to achieve meaningful improvements in muscle performance.

Consistent gains in strength in the early phases of exercise training in PwMS were previously highlighted only by Fimland and colleagues (2010)[6] who assessed strength changes in the ankle plantarflexors after 3 weeks of HIRT. It should be emphasized that both Fimland's and this study employed maximal intensity training in PwMS with mild to moderate clinical disability (EDSS score <6) which may help explain the achievement of significant strength gains early in the training process. Consequently, these findings may not generalize to patients with more pronounced clinical disability. These current findings are supported by a number of studies carried out in healthy subjects which evidenced early strength improvements in the absence of muscle hyperthophy.[26,27] Maximal strength training, beside inducing early adaptations in strength, has been shown to be superior to conventional submaximal strength training at an intensity of 60-70% of 1 RM.[28] Accordingly, Coburn et al. (2006)[29] reported that only 3 sessions of maximal isokinetic training were sufficient to achieve significant enhancement of muscle performance. Initial gains in strength are generally attributed to neural factors such as increased excitability and discharge rates of motor neurons as well as enhanced neural drive to the trained muscles in healthy subjects[27] as well as in PwMS.[6]

In this study early improvements in maximal strength were evidenced both in terms of the PM, which refers to a single point over the RoM, and maxW which portrays the capability of muscles to maintain an adequate level of strength throughout the entire RoM.[30] These findings are in agreement with a previous study performed in healthy subjects where DFs were tested and trained with similar isokinetic protocols[31] and with several reports in PwMS proving HIRT as effective in significantly reducing muscle weakness.[1-3,5,6,16-25] The finding of an increase in maxW beside PM, which is the gold standard in strength testing,[30] may have practical relevance for PwMS since it may positively impact on their physical functioning during the daily living activities. In this perspective, maxW can usefully complement PM in the interpretation of isokinetic findings, adding valuable information for a comprehensive assessment of muscle performance.[14,15,31]

Regarding the issue of reproducibility, it is widely accepted as a prerequisite for better tracking of changes in measurements in research or clinical practice.[32] Establishing the reproducibility of strength measurements in MS is a worthy endeavor in the light of the high day-to-day variability exhibited by these patients.[9] In the present study the analyses of relative and absolute reproducibility performed at baseline through a test-retest procedure over 3 time points, revealed high consistency and precision of PM and maxW measurements obtained from the ankle DFs of PwMS. These findings, while further confirming the established reliability of isokinetic dynamometry,[33] suggest that the strength changes observed in our patients following training are to be viewed as genuine and not a reflection of day-to-day variability of muscle performance typical of PwMS.[9] Although the sample size was relatively small, it is in line with the numbers indicated by Shrout and Fleiss (1989) to be sufficient for providing an estimate of reliability.[10]

Another issue emerging from this study relates to the retention of strength gains at the follow-up. First, it should be noted that significant gains were still apparent in terms of PM, after 12 weeks from the completion of the HIRT program. On the other hand, the maxW values at 10 and 45°/s, although still higher than those measured at baseline, did not reach statistical significance. Thus, whereas PM remains high, maxW is likely to deteriorate faster. This might indicate that the mechanisms responsible for maintaining the overall capacity (reflected by maxW) are not related to those regarding the peak performance. Furthermore, comparison of the present findings with those derived from previous studies is hampered due to the application of different training protocols, outcomes and muscle groups studied.[1-3,5,6,16-25] Regardless of such heterogeneity, our data on the retention of muscle performance at the 12-week evaluation are in line with a previous study in PwMS which found a retention of maximal isometric strength[2] but in disagreement with more recent reports, which observed no significant differences between baseline and follow-up.[25,34] Although in our PwMS the retention of strength was observed for only 2 out of the 4 considered outcomes, this result is still functionally relevant since in healthy subjects a significant decay in muscle performance has been shown to take place already from the third week of inactivity.[35] Whether or not this finding points out to a different retention mechanism between healthy subjects and PwMS is an interesting topic that begs some fresh research. Moreover, since no follow-up data collected at time intervals shorter than 12 weeks are available in MS, further studies investigating the time-course of the detraining process in MS over narrower temporal windows are necessary.

6.5.2 Study Limitations

The primary limitation of this proof-of-concept study is the absence of a control group of healthy subjects or PwMS undergoing no training. Secondly, considering the peculiar features of ankle DFs, the present findings should not be generalized to other body districts.

6.6 Conclusions

In PwMS a 6-week maximal-intensity RT of the ankle DFs induced significant and clinically relevant increases in maximal strength. Interestingly, 3 weeks of training proved sufficient to achieve consistent and meaningful improvements in muscle performance. These findings may have practical dose-response as well as cost-effectiveness implications in the management of muscle weakness of PwMS.

6.7 Table And Figure

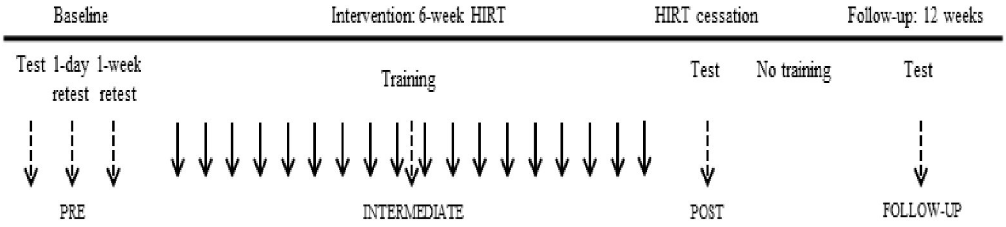


Figure 1. Timeline of the study.

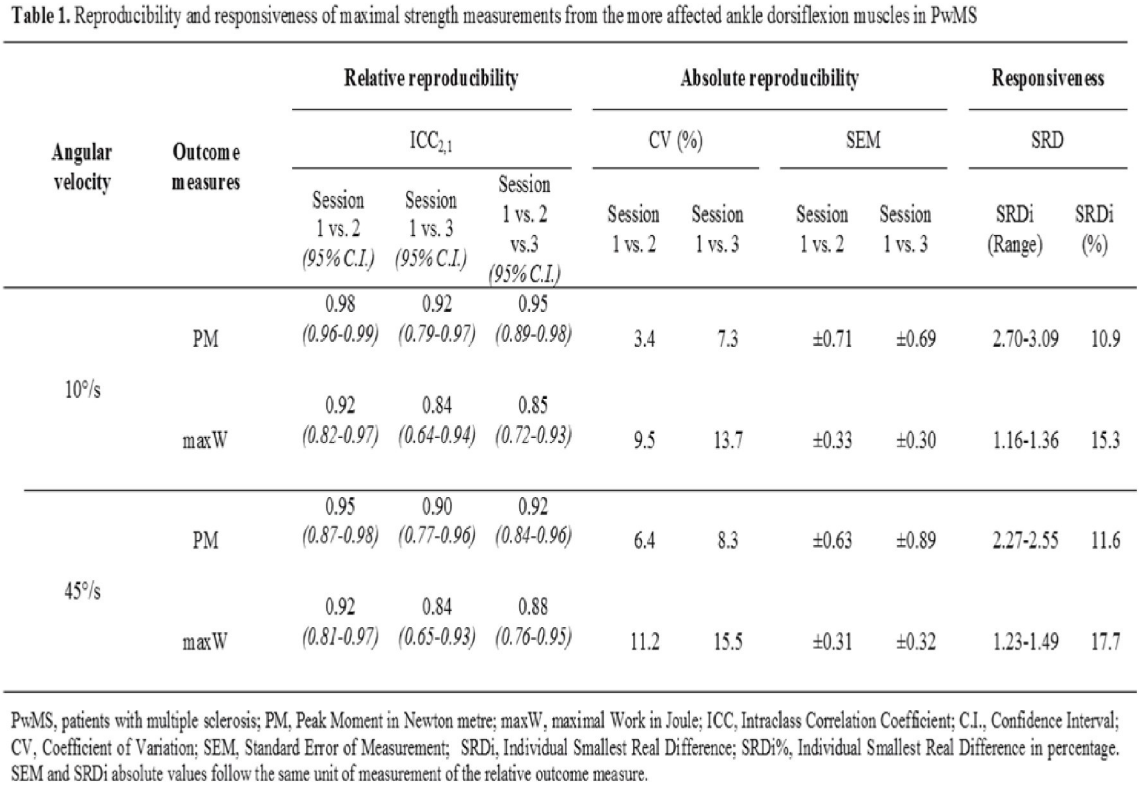
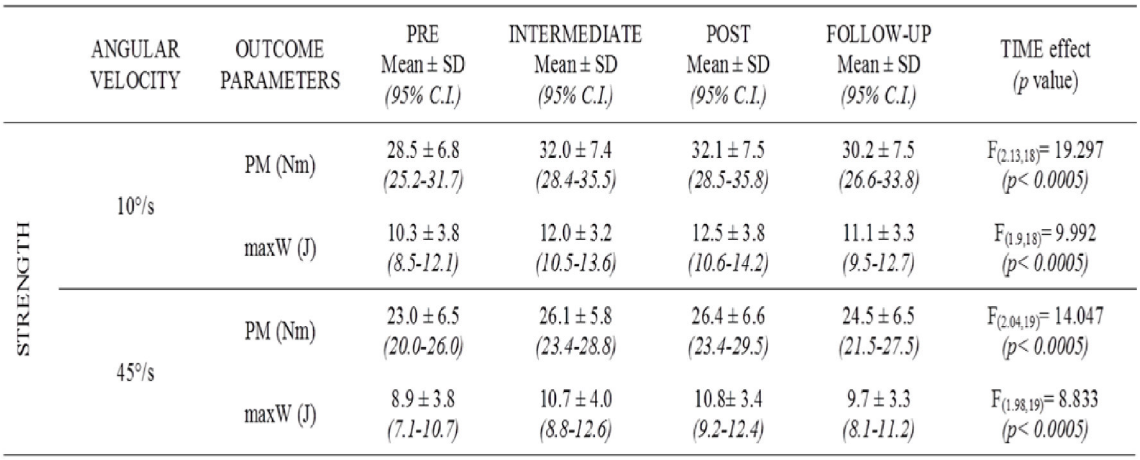


Table 1. Reproducibility and responsiveness of maximal strength measurements from the more affected ankle dorsiflexion muscles in PwMS

Angular velocity	Outcome measures	Relative reproducibility			Absolute reproducibility				Responsiveness	
		$ICC_{2,1}$			CV (%)		SEM		SRD	
		Session 1 vs. 2 *(95% C.I.)*	Session 1 vs. 3 *(95% C.I.)*	Session 1 vs. 2 vs.3 *(95% C.I.)*	Session 1 vs. 2	Session 1 vs. 3	Session 1 vs. 2	Session 1 vs. 3	SRDi (Range)	SRDi (%)
10°/s	PM	0.98 *(0.96-0.99)*	0.92 *(0.79-0.97)*	0.95 *(0.89-0.98)*	3.4	7.3	±0.71	±0.69	2.70-3.09	10.9
	maxW	0.92 *(0.82-0.97)*	0.84 *(0.64-0.94)*	0.85 *(0.72-0.93)*	9.5	13.7	±0.33	±0.30	1.16-1.36	15.3
45°/s	PM	0.95 *(0.87-0.98)*	0.90 *(0.77-0.96)*	0.92 *(0.84-0.96)*	6.4	8.3	±0.63	±0.89	2.27-2.55	11.6
	maxW	0.92 *(0.81-0.97)*	0.84 *(0.65-0.93)*	0.88 *(0.76-0.95)*	11.2	15.5	±0.31	±0.32	1.23-1.49	17.7

PwMS, patients with multiple sclerosis; PM, Peak Moment in Newton metre; maxW, maximal Work in Joule; ICC, Intraclass Correlation Coefficient; C.I., Confidence Interval; CV, Coefficient of Variation; SEM, Standard Error of Measurement; SRDi, Individual Smallest Real Difference; SRDi%, Individual Smallest Real Difference in percentage. SEM and SRDi absolute values follow the same unit of measurement of the relative outcome measure.

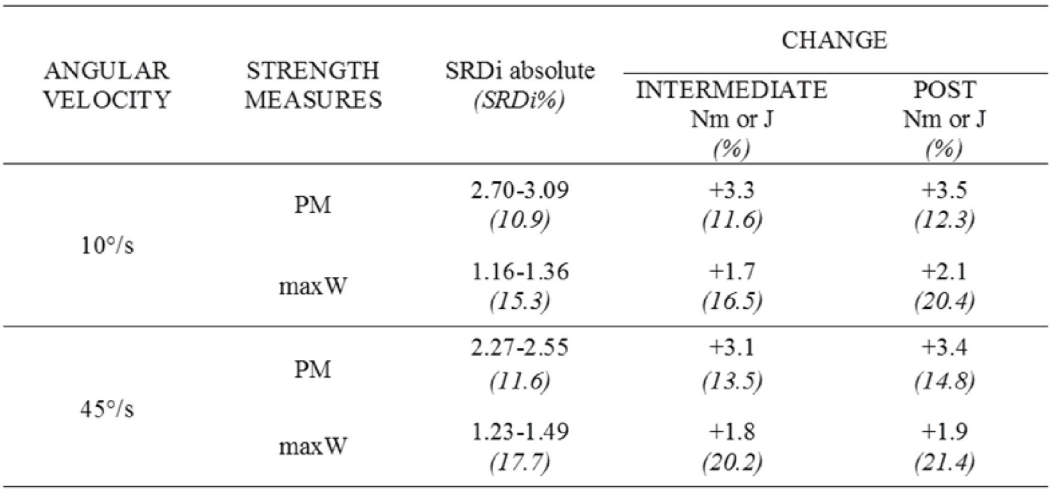
Table 2. Changes in maximal strength before and after a 6-week high-intensity RT of the more affected ankle dorsiflexion muscles in PwMS.



	ANGULAR VELOCITY	OUTCOME PARAMETERS	PRE Mean ± SD *(95% C.I.)*	INTERMEDIATE Mean ± SD *(95% C.I.)*	POST Mean ± SD *(95% C.I.)*	FOLLOW-UP Mean ± SD *(95% C.I.)*	TIME effect (*p* value)
STRENGTH	10°/s	PM (Nm)	28.5 ± 6.8 *(25.2-31.7)*	32.0 ± 7.4 *(28.4-35.5)*	32.1 ± 7.5 *(28.5-35.8)*	30.2 ± 7.5 *(26.6-33.8)*	$F_{(2.13,18)}$= 19.297 *(p< 0.0005)*
		maxW (J)	10.3 ± 3.8 *(8.5-12.1)*	12.0 ± 3.2 *(10.5-13.6)*	12.5 ± 3.8 *(10.6-14.2)*	11.1 ± 3.3 *(9.5-12.7)*	$F_{(1.9,18)}$= 9.992 *(p< 0.0005)*
	45°/s	PM (Nm)	23.0 ± 6.5 *(20.0-26.0)*	26.1 ± 5.8 *(23.4-28.8)*	26.4 ± 6.6 *(23.4-29.5)*	24.5 ± 6.5 *(21.5-27.5)*	$F_{(2.04,19)}$= 14.047 *(p< 0.0005)*
		maxW (J)	8.9 ± 3.8 *(7.1-10.7)*	10.7 ± 4.0 *(8.8-12.6)*	10.8± 3.4 *(9.2-12.4)*	9.7 ± 3.3 *(8.1-11.2)*	$F_{(1.98,19)}$= 8.833 *(p< 0.0005)*

PwMS, patients with multiple sclerosis; RT, resistance training; PM, peak moment; maxW, maximal work; PRE: assessment at baseline; INTERMEDIATE, assessment after 3 weeks of resistance training; POST, assessment at the end of 6-week intervention period; FOLLOW-UP, assessment after 12 weeks from the end of intervention. C.I., confidence interval; main effect of time was calculated by repeated-measures ANOVA and significance level set at p< 0.05.

Table 3. Clinical relevance of the changes in strength after 3 and 6 weeks of resistance training



ANGULAR VELOCITY	STRENGTH MEASURES	SRDi absolute *(SRDi%)*	CHANGE INTERMEDIATE Nm or J *(%)*	CHANGE POST Nm or J *(%)*
10°/s	PM	2.70-3.09 *(10.9)*	+3.3 *(11.6)*	+3.5 *(12.3)*
	maxW	1.16-1.36 *(15.3)*	+1.7 *(16.5)*	+2.1 *(20.4)*
45°/s	PM	2.27-2.55 *(11.6)*	+3.1 *(13.5)*	+3.4 *(14.8)*
	maxW	1.23-1.49 *(17.7)*	+1.8 *(20.2)*	+1.9 *(21.4)*

PM, Peak Moment in Newton metre; maxW, maximal Work in Joule; SRDi%, Individual Smallest Real Difference in percentage; maxW, maximal work; INTERMEDIATE, assessment after 3 weeks of resistance training; POST, assessment at the end of 6-week intervention period.

6.8 References

1. White LJ, McCoy SC, Castellano V, Gutierrez G, Stevens JE, Walter GA, Vandenborne K. Resistance training improves strength and functional capacity in persons with multiple sclerosis. Mult Scler. 2004; 10: 668-674.
2. Dalgas U, Stenager E, Jakobsen J, Petersen T, Hansen HJ, Knudsen C, Overgaard K, Ingemann-Hansen T. Resistance training improves muscle strength and functional capacity in multiple sclerosis. Neurology. 2009; 73: 1478-1484.
3. Hayes HA, Gappmaier E, LaStayo PC. Effects of high-intensity resistance training on strength, mobility, balance, and fatigue in individuals with multiple sclerosis: a randomized controlled trial. J Neurol Phys Ther. 2011; 35: 2-10.
4. Rietberg MB, van Wegen EE, Uitdehaag BM, Kwakkel G. The association between perceived fatigue and actual level of physical activity in multiple sclerosis. Mult Scler. 2011; 17: 1231-1237.
5. Kjølhede T, Vissing K, Dalgas U. Multiple sclerosis and progressive resistance training: a systematic review. Mult Scler. 2012; 18: 1215-1228.
6. Fimland MS, Helgerud J, Gruber M, Leivseth G, Hoff J. Enhanced neural drive after maximal strength training in multiple sclerosis patients. Eur J Appl Physiol. 2010; 110: 435-443.
7. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011; 69: 292-302.
8. Carroll TJ, Herbert RD, Munn J, Lee M, Gandevia SC. Contralateral effects of unilateral strength training: evidence and possible mechanisms. J Appl Physiol *(1985)*. 2006; 101: 1514-1522.
9. Lambert CP, Archer RL, Evans WJ. Muscle strength and fatigue during isokinetic exercise in individuals with multiple sclerosis. Med Sci Sports Exerc. 2001; 33: 1613-1619.

10. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull. 1979; 86: 420-428.
11. Lexell JE, Downham DY. How to assess the reliability of measurements in rehabilitation. Am J Phys Med Rehabil. 2005; 84: 719-723.
12. Guyatt G, Walter S, Norman G. Measuring change over time: assessing the usefulness of evaluative instruments. J Chronic Dis. 1987; 40: 171-178.
13. Harbo T, Brincks J, Andersen H. Maximal isokinetic and isometric muscle strength of major muscle groups related to age, body mass, height, and sex in 178 healthy subjects. Eur J Appl Physiol. 2012; 112: 267-275.
14. Manca A, Solinas G, Dragone D and Deriu F. Isokinetic testing of muscle performance: new concepts for strength assessment. Isokinet Exerc Sci 2015a; DOI 10.3233/IES-15-566.
15. Manca A, Solinas G, Dragone D, Dvir Z, Deriu F. Characterization of ankle dorsiflexors performance in healthy subjects following maximal-intensity isokinetic resistance training. J Electromyogr Kinesiol. Epub ahead of print 17 Jun 2015. doi: 10.1016/ j.jelekin.2015.06.002.
16. DeBolt LS, McCubbin JA. The effects of home-based resistance exercise on balance, power, and mobility in adults with multiple sclerosis. Arch Phys Med Rehabil. 2004; 85: 290-297.
17. 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: 1824-1829.
18. Dodd KJ, Taylor NF, Denisenko S, Prasad D. A qualitative analysis of a progressive resistance exercise programme for people with multiple sclerosis. Disabil Rehabil. 2006; 28: 1127-1134.
19. Taylor NF, Dodd KJ, Prasad D, Denisenko S. Progressive resistance exercise for people with multiple sclerosis. Disabil Rehabil. 2006; 28: 1119-1126.
20. de Souza-Teixeira F, Costilla S, Ayán C, García-López D, González-Gallego J, de Paz JA. Effects of resistance training in multiple sclerosis. Int J Sports Med. 2009; 30: 245-250.

21. Filipi ML, Kucera DL, Filipi EO, Ridpath AC, Leuschen MP. Improvement in strength following resistance training in MS patients despite varied disability levels. NeuroRehabilitation. 2011; 28: 373-382.
22. Sabapathy NM, Minahan CL, Turner GT, Broadley SA. Comparing endurance- and resistance-exercise training in people with multiple sclerosis: a randomized pilot study. Clin Rehabil. 2011; 25: 14-24.
23. Broekmans T, Roelants M, Feys P, Alders G, Gijbels D, Hanssen I, Stinissen P, Eijnde BO. 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.
24. Dodd KJ, Taylor NF, Shields N, Prasad D, McDonald E, Gillon A. 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.
25. Medina-Perez C, de Souza-Teixeira F, Fernandez-Gonzalo R, 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. Moritani T, deVries HA. Neural factors versus hypertrophy in the time course of muscle strength gain. Am J Phys Med. 1979; 58: 115-130.
27. Enoka RM. Neural adaptations with chronic physical activity. J Biomech. 1997; 30: 447-455.
28. Heggelund J, Fimland MS, Helgerud J, Hoff J. Maximal strength training improves work economy, rate of force development and maximal strength more than conventional strength training. Eur J Appl Physiol. 2013; 113: 1565-1573.
29. Coburn JW, Housh TJ, Malek MH, Weir JP, Cramer JT, Beck TW, Johnson GO. Neuromuscular responses to three days of velocity-specific isokinetic training. J Strength Cond Res. 2006; 20: 892-898.
30. Morrissey MC. The Relationship between Peak Torque and Work of the Quadriceps and Hamstrings after Meniscectomy. J Orthop Sports Phys Ther. 1987; 8: 405-408.

31. Manca A, Pisanu F, Ortu E, Natale ER, Ginatempo F, Dragone D, Tolu E, Deriu F. A comprehensive assessment of the cross-training effect in ankle dorsiflexors of healthy subjects: A randomized controlled study. Gait Posture. 2015; 42: 1-6.
32. Hopkins WG. Measures of reliability in sports medicine and science. Sports Med. 2000; 30: 1-15.
33. Gleeson NP, Mercer TH. The utility of isokinetic dynamometry in the assessment of human muscle function. Sports Med. 1996; 21: 18-34.
34. Dalgas U, Stenager E, Lund C, Rasmussen C, Petersen T, Sørensen H, Ingemann-Hansen T, Overgaard K. Neural drive increases following resistance training in patients with multiple sclerosis. J Neurol. 2013; 260: 1822-1832.
35. Bosquet L, Berryman N, Dupuy O, Mekary S, Arvisais D, Bherer L, Mujika I. Effect of training cessation on muscular performance: a meta-analysis. Scand J Med Sci Sports. 2013; 23: 140-149.

Study 7: The effect of contralateral strength training on muscle weakness in people with multiple sclerosis: a proof-of-concept case series.

7.1 Abstract

Background The contralateral strength training (CST) effect is a transfer of muscle performance to the untrained limb following training of the contralateral side.

Objective To explore, in individuals with MS presenting a marked lower limb strength-asymmetry, the effectiveness of CST on muscle weakness of the more-affected limb (MA), following training of the less-affected limb (LA).

Design Single-subject research design.

Methods Eight individuals with MS underwent 16 to 18 high-intensity training sessions of the LA ankle dorsiflexion muscles (DF). The primary outcome of this single-system case series was maximal strength expressed as peak moment and maximal work. Secondary outcomes were: 6-Minute-Walking Test; Timed-Up-and-Go; 10-Meter-Timed-Walk.

Results After the 6-week intervention, the contralateral MA untrained limb showed a 22-24% increase in maximal strength (p <0.01). From PRE to POST, participants performed significantly better (p <0.05) also in the clinical and functional secondary outcomes. At the 12-week follow-up, the strength levels of the weaker untrained limb remained significantly superior to baseline in the majority (5 out of 8) of the outcome parameters.

Limitations Considering the design employed and the sample size, these findings should be cautiously generalized and will need confirmation in a properly planned randomized controlled trial.

Conclusions The present proof-of-concept study shows for the first time the occurrence of the CST-effect on muscle performance of ankle DF in participants with MS. These preliminary findings disclose new potential implications for CST as a promising rehabilitation approach to those conditions where unilateral muscle weakness does not allow or makes difficult performing a conventional strength training of the weaker limb.

7.2 Introduction

Multiple sclerosis (MS) is a neurological condition characterized by reduced muscle strength during both dynamic and static muscle contractions.[1] Compared to matched healthy subjects, participants with MS present a decreased ability to fully activate motor units (47-93% *versus* 94-100%) in the lower limb muscles,[2] with an overall reduction of force development ranging from 30 to 40%.[3] Muscle weakness severely affects the lifestyle of participants with MS reducing their ability to perform even relatively mild physical exercise,[4] with a consequent decrease in the level of daily living activities (ADL).[3]

Evidences have shown that resistance training has a significant positive effect on ADL in people with MS, resulting in increased quality of life (QoL).[5] Despite the effects of resistance training on walking performance are still inconclusive,[5] it has proved effective in significantly reducing muscle weakness,[3] potentially improving balance[7] and inducing a remarkable decrease in self-reported fatigue.[8]

In rehabilitation, when strength impairment is prominently lateralized to one limb, resistance training is conventionally addressed to the weaker side in order to balance the deficit. However, such standard approach may not always be applicable to a severely weakened limb that is too compromised to sustain it.[9] For those participants presenting with a predominantly unilateral hyposthenia, in whom training the more-affected (MA) limb is not initially possible, contralateral strength training (CST) may represent a viable alternative to the conventional direct approach. The CST-effect, also known as cross-education,[10] refers to an inter-limb phenomenon whereby exercise on one limb can induce a transfer of strength or skills to the contralateral untrained side.[11] Extensively studied in healthy subjects[11,12] and in orthopedic conditions,[13,14] it is surprisingly almost unaddressed in neurological disorders. In this regard, only two studies tested the CST in stroke hemiparesis, where significant strength increases were observed, respectively, in the ankle dorsiflexion muscles (DF)[15] and in the wrist extensors[16] of the paretic untrained limb after training of the contralateral unaffected side. Another report tested successfully the **CST** in a single case of peripheral nerve injury.[17] No studies have investigated so far the potential of the **CST** in participants with MS.

With these considerations in mind, it was hypothesized that, also in individuals with MS, a CST of the ankle DF of the less-affected limb might induce a transfer of performance to the more-affected untrained homologous muscles. If confirmed, this study would carry clinical implications in the rehabilitation of unilateral impairments induced by neurological conditions.[15-17]

The main purpose of this trial was, therefore, to investigate the occurrence and magnitude as well as the meaningfulness of the CST-effect in selected participants with MS presenting with a predominantly unilateral hyposthenia. To this aim the peak moment (PM) and maximal work (MW) were set as the primary outcomes. Secondly, clinical and functional outcomes were also investigated.

7.3 Materials and methods

7.3.1 Subjects

Participants with a predominantly unilateral strength impairment of the ankle DF were selected from those referring to the Multiple Sclerosis Centre of the University of Sassari for periodical clinical and neurophysiological evaluations. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional Bioethics Committee of the Local Health Authority (ASL n.1-Sassari, Italy; Prot. number 1160/L/2013). A written informed consent was obtained by all the participants before enrollment.

Inclusion criteria were: diagnosis of MS (according to 2010 revision of diagnostic criteria[18]); age 18 years or over; evidence of strength asymmetry between ankle dorsiflexion muscles (patient-reported, then verified at the baseline assessment by isokinetic dynamometry as a least difference between sides ≥20%); independent ambulation with or without use of unilateral assistance; Expanded Disability Status Scale (EDSS) ≤6, with Pyramidal Functional System score ≥3.

Exclusion criteria were: any medical condition contra-indicating participation in strength training exercises; disability and comorbidities caused by other medical conditions and not related to MS; occurrence of relapses, treatment with corticosteroid and/or botulinum toxin, variations in Disease-Modifying Drugs (DMD) or symptomatic treatment within 6 months prior to recruitment; severe ataxia and postural instability (assessed with Berg Balance Scale, cutoff value for exclusion: ≤35); major depression (assessed with Beck Depression Inventory-BDI scale, cutoff for exclusion: ≥28; clinically relevant cognitive deficits (assessed with Frontal Assessment Battery-FAB scale, cutoff for exclusion: ≥14 and with the Trail Making-TMT Test A and B, cutoffs for exclusion: A ≥78 sec. and TMT B ≥273 sec.); participation in rehabilitative or training programs within 6 months prior to the study. A team of neurologists and neurophysiologists performed all the clinical examinations and testing procedures (MPC, EO, IRZ, ERDN). Two of them (MPC, IRZ) were assigned the eligibility of the participants and their eventual enrolment in the study.

Participants deemed eligible underwent clinical, functional and dynamometric assessments within a 2-week period. Subjects were asked to refrain from any other exercise activity for the entire duration of the study.

7.3.2 Design

The design of the study is illustrated in Figure 1. A series of 8 replicated single-system case studies was completed employing a pretest-posttest design with a short-term follow-up, which is an implementation of the simple one-group pretest-posttest study.[19] It is also known as AB design with follow-up, where A represents the baseline assessment and B refers to the intervention phase. The outcome measure is recorded repeatedly over both phases. The timeline of the study, which was articulated in 4 phases, is shown in Figure 1. The study design was implemented employing multiple pretests to control for maturation which is frequently associated with strength testing protocols.[18]

7.3.3 Muscle Strength Testing

Muscle performance of the ankle DF was unilaterally assessed on both legs with an isokinetic dynamometer (Biodex System 3, Biodex Medical Systems, Shirley, NY, USA). The subject was positioned onto the isokinetic device with the knee flexed at 30° and the ankle in full plantar flexion taken as starting position.[20] Subject positioning was firmly secured to the dynamometer with supplied straps. Before baseline, participants were familiarized with the isokinetic strength testing protocol to minimize the potential effects of learning associated to this procedure.[9]

All subjects underwent a predefined 5-minute warm-up. Following a 5-min rest the criterion test took place consisting of 4 repetitions at 45°/s and 2 repetitions at 10°/s. The LA leg was tested first. A 6-min rest elapsed between the testing of the LA and MA leg.

7.3.4 Clinical and functional assessment

Walking ability in ADL was assessed using the 6-Minute Walk Test (6MWT), the 10-Metre Timed Walk (10MTW) and the Timed Up and Go (TUG), which have been proved as highly reliable mobility tests in individuals with MS.[21-23] QoL (estimated by MSQoL-54) was also assessed.

7.3.5 Intervention

Participants sustained a strength training program consisting of a 6-week maximal-intensity isokinetic concentric resistance training of the LA ankle DF, with a 3 sessions/week frequency. Subjects sustained 3 sets of 4 maximum repetitions (RM) at 45°/s of angular velocity and 3 sets of 4 RM at 10°/s, with a 3-min rest given between sets. Each session lasted approximately 25 minutes. A maximal rather than a submaximal exercise protocol was chosen to optimize the training-induced neural adaptations[24,25] which are acknowledged as the main neurophysiological underpinnings of cross-education.[9,11] When a session was missed, subjects were allowed to recover it at the end of the cycle to ensure that at least 16 out of the scheduled 18 sessions were accomplished.

7.3.6 Data analysis

Statistical analysis was performed using the SPSS software for Windows, version 18.0 (SPSS Inc, Chicago, IL - USA).

Test-retest reproducibility was estimated by calculating two different numerical indices: 1) *Intraclass correlation coefficient* (ICC), which is generally accepted as the preferred method of quantifying relative reproducibility, using a 2-way random $ICC_{2,1}$ for single measures.[26] The ICC analysis was applied over 3 time points (test; 1-day retest; 1-week retest) for the primary outcomes (PM; MW) and over 2 time points (test; 1-day retest) for 2 out of the 3 clinical and functional outcomes (10MTW; TUG), while reliability of the 6MWT was not assessed due to fatigue concerns; 2) *Coefficient of variation* (CV), which is an index of absolute reproducibility and is employed to interpret the consistency of measurements across time. It was calculated as a percentage: $CV\% = (\text{method error}/\text{mean}) * 100$, where method error= $SD_{diff}/\sqrt{2}$.[27]

Data were processed employing a dual approach: *group*- and *individual*-level analyses.

Group-level analysis – PM and MW were analyzed with a repeated-measures ANOVA using Time (PRE, INTERMEDIATE, POST and FOLLOW-UP) and Side (LA/trained and MA untrained) as factors. For the Time factor, only the highest values in PM or MW at each single time point was recorded and kept for the statistical analysis. When significance was achieved, pairwise comparisons with Bonferroni adjustment were used. Pairwise mean differences were estimated by the linear contrasts of the repeated-measures ANOVA and their confidence intervals. To compare the differences we used a separated model for each side. If significant main effects or interactions were detected, simple main effects analysis followed using one-way ANOVA or dependent *t*-tests when appropriate.

The 6MWT, 10MTW and TUG were analyzed using a repeated-measures ANOVA using Time as one-way factor.

Individual-level analysis – The two-standard deviation (2SD) band method was employed to quantify the visual findings.[19] The smallest real difference (SRD), which is a measure of responsiveness and is defined as the smallest change in score that exceeds the error of measurement and may thus be recognized as clinically meaningful at the level of the individual patient,[28] was also calculated. The individual SRD (SRDi) was calculated according to the following formula: SRDi = 2.77*rms (2)*rms (1-ICC) and reported also as SRDi% calculated by 2.77 x (SRDi/grand mean) x 100, where grand mean represents the mean of the three testing sessions. A difference score (DS) was calculated as the difference between the value in PM or MW recorded at the intermediate assessment *versus* baseline (3-week DS) as well as that recorded at the POST assessment *versus* baseline (6-week DS) but also as that recorded at the FOLLOW-UP assessment *versus* baseline (12-week DS). Each DS was calculated individually and was then compared to the absolute SRDi and to the SRDi% score. The SRD analysis was also applied to evaluate any change in the clinical and functional outcomes (10MTW; TUG).

7.4 Results

All participants (39.5±12.14 years old) had a diagnosis of definite MS with a mean disease duration of 11.37±5.88 years. In our sample, neurological examination revealed 3 out of 8 participants (#6, 7 and 8) exhibiting a drop foot disorder of gait. On average participants had a moderate disability (median EDSS: 3.5), absence of depression (BDI: 11.3±6.2) and normal cognitive functions with special regard to the attentive (median TMT B-A: 44.7 seconds) and executive (FAB: 16.6±1.5) domains. Compared to the most recent normative values of maximal strength obtained from healthy subjects under isokinetic conditions,[29-31] participants in this study exhibited lower levels of muscle performance.

Demographic and clinical characteristics are reported for each patient in Table 1. No relapses or changes in medications occurred during the study. The results of the reproducibility and responsiveness analyses are detailed in Table 2. Overall, at both velocities, all ICCs for relative reliability were ≥ 0.80 while the CV%, calculated for absolute reliability purposes, ranged 1.5-14.7%, with a median value of 8.4%.

7.4.1 Group results

Muscle strength – In all subjects the MA limb was significantly weaker than the LA limb both in terms of PM and MW at 10 and 45°/s of angular velocity (all p values < 0.03). Subject 8 was excluded by group-level analysis since she only underwent isometric testing due to inability to generate functional dorsiflexion with the MA limb under isokinetic conditions. Following training, a significant main effect of time was detected both in PM and MW at 10°/s (PM: $F_{3,33}=17.65$; $p<0.0005$; MW: $F_{3,33}=14.03$; $p<0.0005$) as well as at 45°/s (PM: $F_{3,33}=15.01$; $p<0.0005$; MW: $F_{3,33}=23.03$; $p<0.0005$).

However, the trained and untrained limbs improved in such a similar manner over time that no significant time by side interaction was observed at 10°/s (PM: $F_{3,33}$=1.078; *p*=0.37; MW: $F_{3,33}$=0.923; *p*=0.44) and 45°/s (PM: $F_{3,33}$=0.375; *p*=0.77; MW: $F_{3,33}$=1.018; *p*=0.40). Average PM and MW results at the different time points of the study are detailed by side and angular velocity in Table 3. Regarding the directly-trained LA limb, significant PRE to POST changes for all dynamometric variables at 45°/s and 10°/s (Table 3) were found. Significant PRE-POST improvements were also detected in the untrained MA limb, depicting a CST-effect.

At the follow-up, a pattern of detraining was evidenced in the 2 limbs by the significant deterioration of muscle performance compared to POST. However, strength levels remained significantly superior to baseline values in the majority of the outcome parameters (5 out of 8), revealing a consistent retention of muscle performance after 12 weeks from the training completion (Table 3).

Clinical and functional outcomes – Test-retest reliability for the mobility measures proved excellent for both the 10MTW (ICC=0.99) and TUG test (ICC=0.98). Due to the high degree of fatigue that the 6MWT induced in most of the participants at the baseline assessment, the retest for reliability purposes was not carried out in order to avoid potential fatigue-induced interferences that would have affected the planned training schedule.

The repeated-measures ANOVA revealed a main effect of time for the 10MTW ($F_{2,14}$= 5.165; *p*=0.02) and the TUG test ($F_{2,14}$= 6.405; *p*=0.01). No significant effect of time was detected for the 6MWT ($F_{2,14}$= 0.568; *p*=0.50). Pairwise comparisons revealed significant PRE to POST improvements in 10MTW (-9.7%; *p*= 0.03) and TUG (-11.3%; *p*= 0.04) tests while only a trend towards improvement was observed in the 6MWT which failed to achieve statistical significance (+8%; *p*= 0.09) (Table 4). The observed improvements were not maintained at the 12-week follow-up.

The analysis of the SRD that could be applied only to 10MTW and TUG, revealed for both outcomes training-induced changes greater than the SRD values which served as cutoffs for clinically meaningful changes (Table 4).

No change in the overall quality of life as measured by MSQol-54 Phys H (PRE: 56.8±20.3; POST: 60.0±18.7; *p*=0.12) and by the MSQol-54 Mental H (PRE: 67.9±21.2; POST: 67.7±24.2;*p*=0.96) was detected.

7.4.2 Individual results

Individual-level results are reported for muscle strength, which was the only variable suited to be repeatedly assessed throughout the entire duration of the study. To adhere to the cross-education paradigm,[11] during the training period (phase B of the study) strength measurements were carried out in each training session only in the LA trained limb, while only one single intermediate assessment was performed in the MA untrained limb in the middle of the intervention period (Figure 1).

Muscle performance of the ankle DF of both sides is reported for subjects 1-8 in terms of PM (Fig. 2) and for subjects 1-7 in terms of MW (Fig. 3) since MW calculations were not possible for Subject 8 (see above). Figures 2 and 3 show the individual responses to the intervention throughout the entire duration of the study. The visual analysis of trend, level and slope of the curves revealed visible PRE-POST improvements in the majority of the sample.

The results of the 2SD band analysis, which was applied to the LA trained side only, are detailed in Table 5 and displayed in Figures 2 and 3 (left panels). Data showed that all dynamometric parameters significantly improved in 3 of 7 participants (42.8%, Subjects 1, 2, 4). Two of 7 participants (28.6%, Subjects 6 and 7) exhibited a significant improvement of at least 3 of 4 parameters. In 2 of 7 participants (28.6%, Subjects 3 and 5) all parameters improved without reaching statistical significance.

Visual inspection of data obtained from the MA untrained ankle DF (Figures 2 and 3, right panels) showed the occurrence of the CST-effect in all participants except Subject 3. With specific regard to Subject 8, the isometric PM showed consistent improvements in both limbs.

The visual inspection analysis and the 2SD band method were complemented by the appraisal of the minimum detectable change expressed as the individual smallest real difference (SRDi) to discriminate relevant from irrelevant changes following an intervention. Table 6 details the comparison between the SRDi cutoff values calculated for each outcome measure at baseline and the changes occurred at each assessment during and after the 6-week CST intervention. Table 7 reports the analysis of SRDi by outcome measure and by side, considering how many participants were capable to exceed the cutoff values for meaningful change after 3 and 6 weeks of CST and at the 12-week follow-up.

7.5 Discussion

This proof-of-concept study explored, in participants with MS presenting with a predominantly unilateral hyposthenia of the lower limbs, the effects of a resistance training of the LA ankle DF on muscle performance of the MA untrained limb. This was achieved employing a dual statistical approach: group- and individual-level analyses.

7.5.1 Group-level analysis

In individuals with MS, a 6-week isokinetic resistance training proved effective in inducing significant increases in muscle performance of the directly trained LA limb, both in terms of PM and MW. These findings are in agreement with a previous study that investigated, in healthy subjects, the effects of a similar isokinetic training regimen on the same variables,[12] and with several reports portraying strength training as effective in significantly reducing muscle weakness in MS.[3,6,7,8]

The training of the LA ankle DF induced a significant transfer of maximal strength to the MA untrained limb, depicting a CST-effect which, to our knowledge, is here reported for the first time in individuals with MS.

The magnitude and temporal development of the direct and indirect gains in strength exhibited, respectively, by the less and more affected limbs was quite similar. This finding may explain the lack of any Time by Side interaction. Such results are surprising since it is generally accepted that the gain of strength in the untrained limb is a 25-50% fraction of that in the trained one.[10,11] However, they are consistent with previous studies performed in healthy subjects where a high-intensity training was employed in the same muscle group[12] or in upper limbs.[14] Interestingly, the crossed transfer of muscle performance was here evidenced not only in terms of PM but also of MW, which is the average measure of the torque output throughout the entire range of motion and is considered a better indicator of muscle function than PM.[32,33] In this perspective, our findings may prove of particular interest in rehabilitative settings.

It should be pointed that the participants enrolled in the present study exhibited differences in the level of performance at baseline, both in terms of PM and MW. However, in single-system designs each participant acts as her/his own control. Regardless of whether the initial level of strength of each participant was high or low, the majority of our participants performed significantly better following the intervention.

The observed strength improvements were also associated to significant increases in all the mobility and walking performance outcome measures. This is in line with the current opinion that resistance training leads to improvement of not only muscular strength but also functional outcomes.[6,34]

The training-induced improvements in maximal strength were also found to be significantly retained in the majority of the dynamometric outcomes considered by the directly-trained LA limb and also by the MA untrained limb after 12 weeks from the end of the intervention period, suggesting that bilateral changes in muscle performance induced by unilateral training proved to be stable and persistent. However, no further improvements were made after the completion of the intervention and, as expected with training protocols, a significant pattern of strength deterioration was observed from POST to FOLLOW-UP was observed, suggesting a causal relationship between the observed effects and the intervention administered. The consistent deterioration of muscle performance which occurred at the cessation of the training might indicate the need for the prolongation of training in order to truly retain the achieved gains.

7.5.2 Individual-level analysis

Causality between the unilateral intervention and the observed bilateral effects was verified at the individual level by the visual inspection of every single response to training exhibited by both limbs of each subject. A clear pattern towards improvement in the levels of maximal strength was visually detectable in the LA limb of all subjects and statistically confirmed by the 2SD-band method in 6 of them (75%). The visual inspection of data obtained from the MA untrained limb revealed an indirect increase in strength, depicting a CST-effect, in 7 of 8 participants (87%). One subject (No. 3) did not show either direct or indirect responses to training. This lack of effects was attributed to poor collaboration observed during the intervention likely due to a certain degree of mood alteration (BDI = 22) which may have affected her involvement in the study.

Visual inspection was complemented by the calculation and analysis of the individual smallest real difference (SRDi) which is a measure of responsiveness and serves as a cutoff value to discriminate relevant from irrelevant changes.[28] While after 3 weeks of CST none of the changes exceeded the cutoffs in both limbs, at the end of the intervention the observed increases in strength were superior to the cutoff values of SRDi for clinically meaningful changes in both the trained and untrained ankle DF. Judging by the stringent standards of SRDi cutoff scores (both absolute and relative), following the 6-week intervention at least 70% of the participants demonstrated an improvement that exceeded the cutoff value in the directly trained ankle DF as well as in the untrained non-dominant side. Moreover, at the 12-week follow-up, more than 50% of the sample showed levels of strength in both sides that were superior to baseline. These findings of good responsiveness, which indicates clinical important changes and corroborates the significance of the adaptations due to training, may have practical dose-response and cost-effectiveness implications when defining the training amount to be prescribed to achieve meaningful improvements in muscle performance and, also, how much change needs to be achieved to induce a meaningful cross-education effect.

7.5.3 Strengths and limitations of the study

The single-system research design chosen for this study is routinely employed to document patterns of clinical change and is considered an appropriate methodology to observe changes in a subject's performance over time, providing clinically relevant information about individual subjects.[35] It is of particular value in evaluating clinical practice or preliminarily exploring the effects of specific treatments for specific problems.[36] However, findings of single-system design studies should be cautiously generalized, since they are considered relatively weak in differentiating coincidence from causality,[37] particularly because they do not include a control group which is essential to discriminate causality from random and familiarization or learning effects. Therefore, further properly planned controlled trials are required to test the clinical relevance and effectiveness of CST.

To adhere to the cross-education paradigm, repeated multiple assessments were not performed in the MA untrained limb during the intervention period. Thus, it was not possible to employ the 2SD-band method to statistically confirm the visual findings from the MA untrained limb.

Following training most of the participants exhibited direct improvements in the trained ankle DF and indirect "crossed" improvements in the untrained homologous muscles which, however, did not translate into changes in QoL. This finding was expected since the participants showed at baseline a mild-to-moderate degree of disability, were fully ambulant, independent and their DF impairment poorly interfered with gait, balance and, in general, QoL. It should also be considered that participants underwent the training of the ankle DF which are a small muscle group possibly playing a minor role in the overall QoL in our sample that exhibited a quite acceptable at the time of enrolment.

A point of strength of this study may reside in the comprehensive assessment of maximal strength not only in terms of PM, as conventionally achieved, but also of MW, which, being a better indicator of muscle function than PM, may help unveiling the full potential of a CST approach as a rehabilitative strategy for muscle weakness in selected participants with MS presenting unilateral muscle weakness.

7.6 Conclusions

The novel finding of this study is the occurrence of the CST-effect in MS which took place in terms of significant and persistent crossed-transfer to the MA untrained ankle DF of maximal strength which also translated into consistent improvements of mobility and walking performance. The present findings contribute to the accumulating evidence portraying CST as a novel and viable approach with potential practical implications in the rehabilitation of unilateral impairments induced by neurological conditions.[15-17] In this perspective, the enhanced muscle performance initially induced by CST in a highly compromised limb may be further implemented and consolidated by extending the duration of the same training protocol or, if possible, by switching to a direct and more conventional training of the weaker side.

7.7 Table And Figure

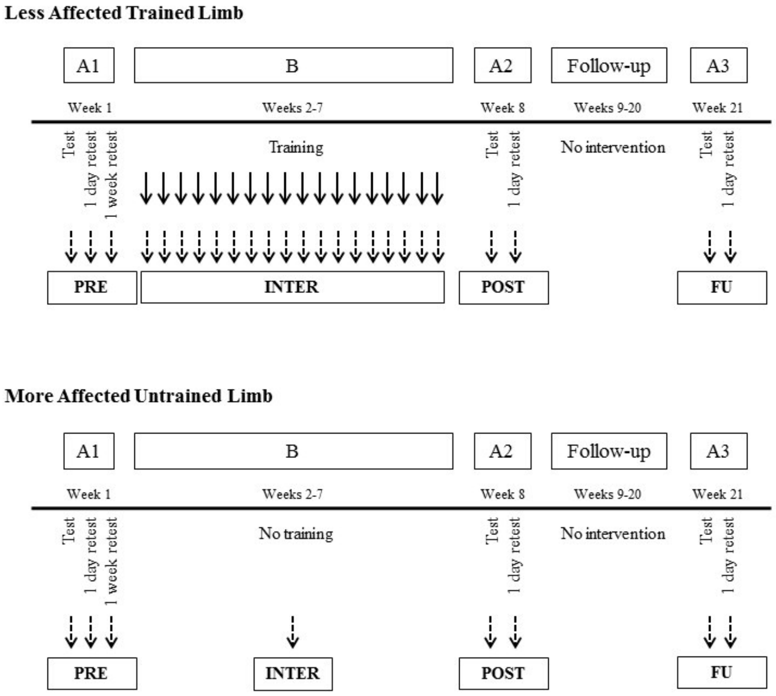


Figure 1. Time line of the study.

A1: pre-training phase with test-retest procedures consisting of 3 bilateral measurements (test, 1-day and 1-week retests) of maximal strength (peak moment and maximal work at 10 and 45°/s angular velocity) from the dorsiflexion muscles (DF) of both sides. B: intervention phase consisting of a 6-week training (3 sessions/week) of the less-affected (LA) ankle DF (upper panel), while leaving the more-affected limb untrained (lower panel). According to the cross-education paradigm,[11] during phase B, multiple measurements (one for each of the 18 scheduled sessions) of maximal strength were obtained only from the LA trained limb (upper panel), while performing only one single measurement (Intermediate, INTER) in a separate session after completing 3 weeks of training in the middle of phase B, from the untrained more-affected ankle DF. A2: post-training test-retest procedures where 2 measurements (test, 1-day retest) of maximal strength were performed in both limbs within one week from the end of phase B. Follow-up: 12-week period of follow-up, with no intervention administered for both limbs. A3: 2 assessments (FU) as in phase A2, carried out within one week after the follow-up period. Arrows with continuous line indicate each resistance-training session administered to the LA ankle DF. Arrows with dashed line indicate the number of assessments performed in both limbs in phase A1 (PRE: baseline assessments), B (Intermediate), A2 (POST), A3 (FU).

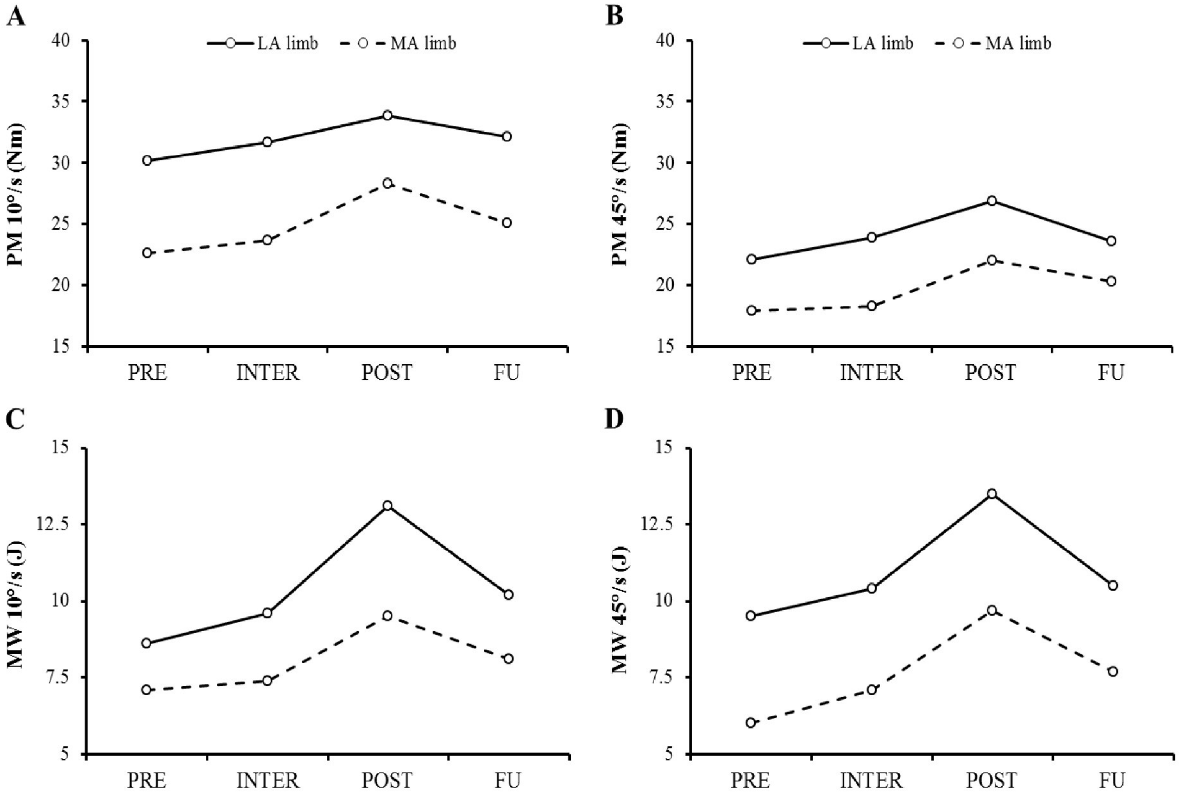


Figure 2. Changes in maximal strength following a 6-week high-intensity resistance training of the less-affected ankle dorsiflexion muscles in patients with multiple sclerosis. Changes in peak moment (PM) and maximal work (MW) are reported by angular velocity at 10°/s (A and C, respectively) and 45°/s (B and D, respectively) for the less-affected trained limb (continuous line) and for the more-affected untrained limb (broken line). PRE, assessment at baseline; INTER, intermediate assessment after 3 weeks of resistance training; POST, assessment at the end of 6-week intervention period; FU, follow-up assessment after 12 weeks from the end of intervention.

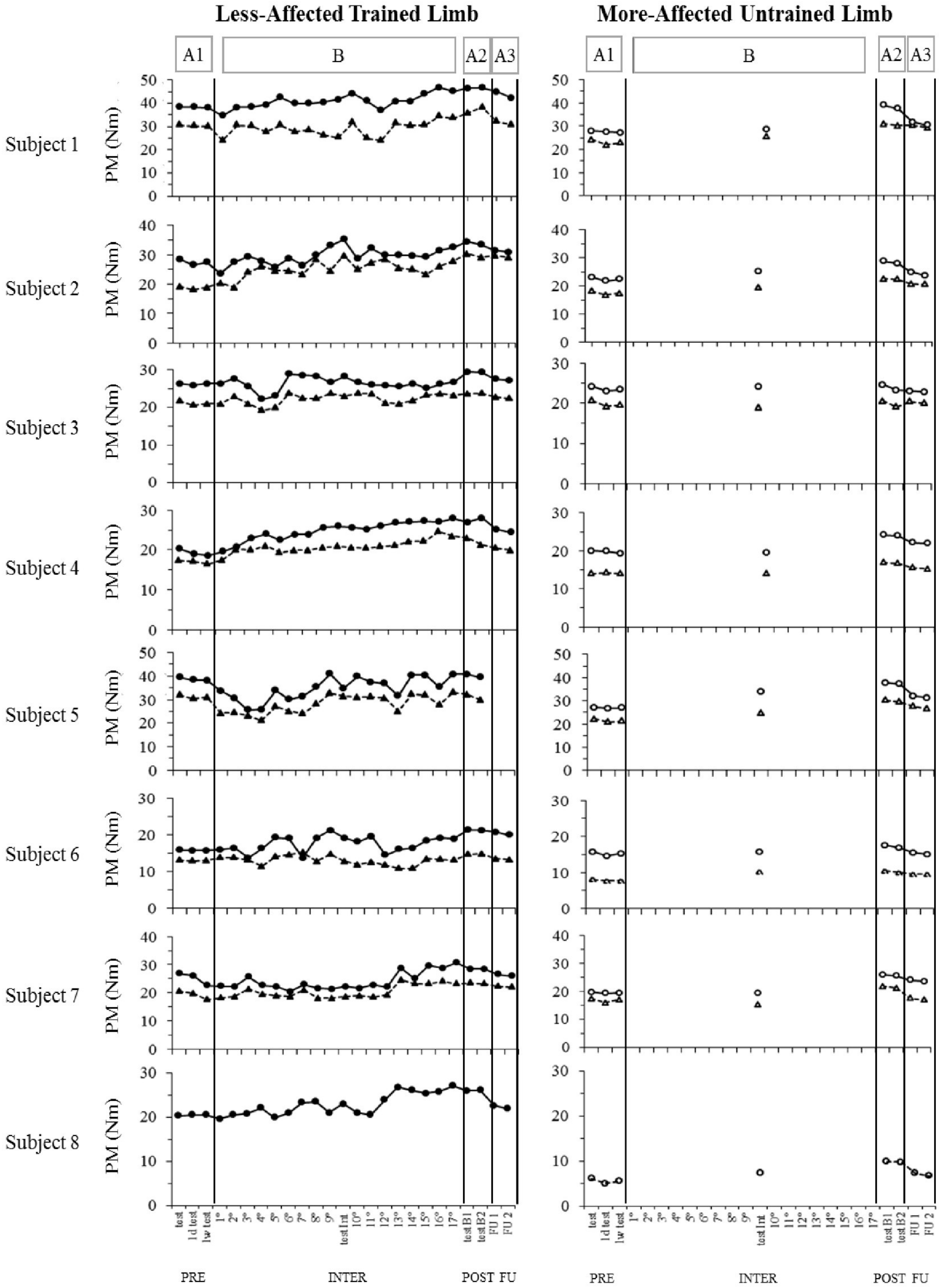

Less-Affected Trained Limb
More-Affected Untrained Limb
A1
B
A2
A3
Subject 1
Subject 2
Subject 3
Subject 4
Subject 5
Subject 6
Subject 7
Subject 8
PM (Nm)
0
10
20
30
40
50
test
1d test
1w test
1°
2°
3°
4°
5°
6°
7°
8°
9°
test Int
10°
11°
12°
13°
14°
15°
16°
17°
test B1
test B2
FU 1
FU 2
PRE
INTER
POST
FU

Figure 3. Effects of a 6-week unilateral resistance training on the peak moment recorded from both the less-affected trained and more-affected untrained ankle dorsiflexors: individual results. The graphs report individual-results obtained in all phases of the study (A1: PRE; B: INTER; A2: POST; A3: FU) for the peak moment (PM) at 45°/s (continuous line) and at 10°/s (dashed line). To adhere the cross-education paradigm,[11] during the intermediate phase B the PM was assessed in each of the 16-18 training sessions in the trained limb (left panel), while a single intermediate measurement was performed, in the middle of the intervention period, in the untrained limb (right panel). Being the PM values of each subject quite different at baseline, in each graph the ordinates are enhanced to emphasize as much as possible the variations of PM throughout the entire duration of the study. Missing points during phase B indicate that subjects #1 and 4 missed the last training session. Missing points during phase A3 indicate that subject #5 missed the follow-up assessment due to drop-out.

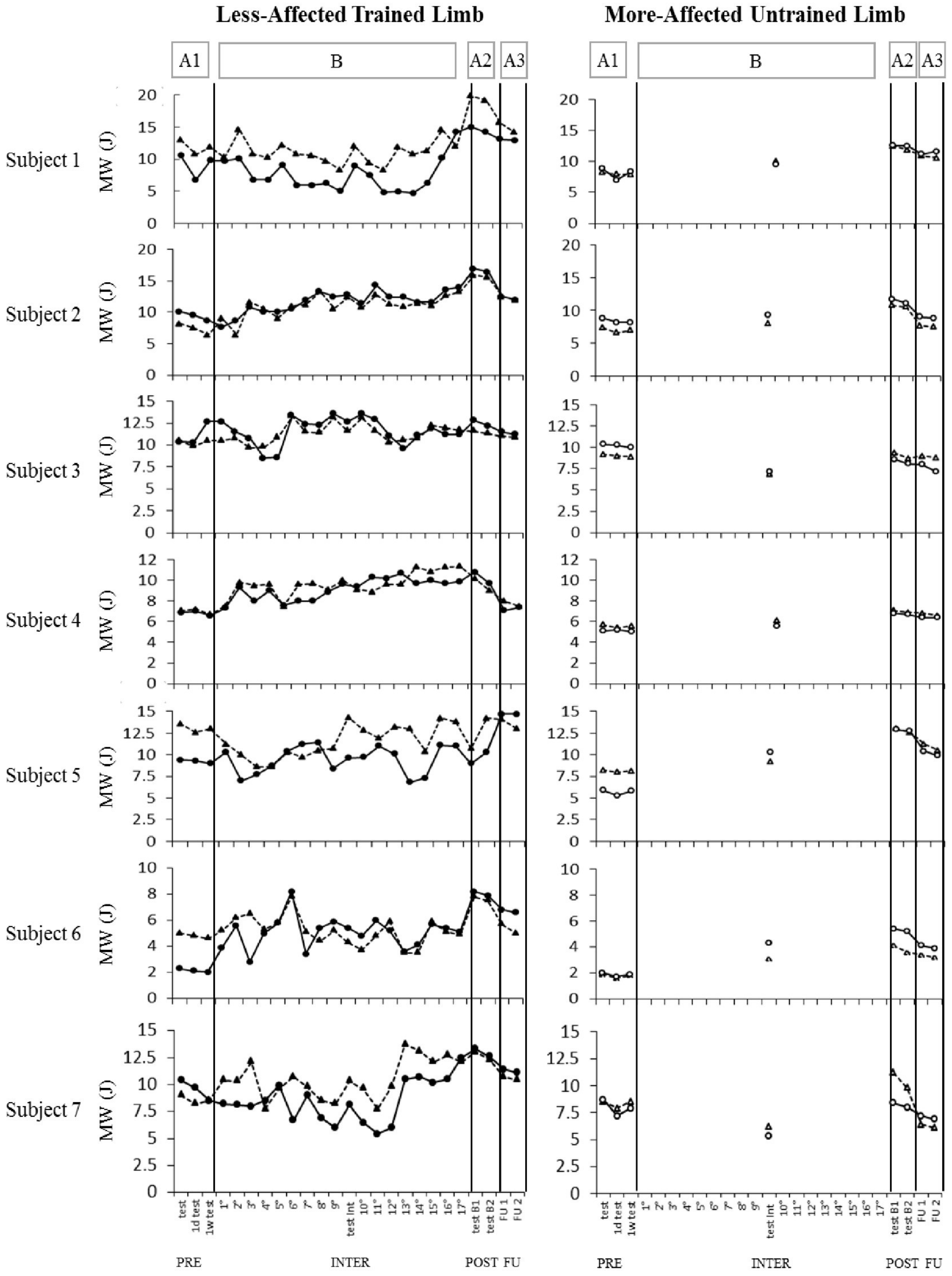

Less-Affected Trained Limb
More-Affected Untrained Limb
A1
B
A2
A3
Subject 1
Subject 2
Subject 3
Subject 4
Subject 5
Subject 6
Subject 7
MW (J)
0
2
2.5
4
5
6
7.5
8
10
12
12.5
15
20
test
1d test
1w test
1°
2°
3°
4°
5°
6°
7°
8°
9°
test Int
10°
11°
12°
13°
14°
15°
16°
17°
test B1
test B2
FU 1
FU 2
PRE
INTER
POST
FU

Figure 4. Effects of a 6-week unilateral resistance training on the maximal work recorded from both the less-affected trained and more-affected untrained ankle dorsiflexors: individual results. The graphs report individual-results obtained in all phases of the study (A1: PRE; B: INTER; A2: POST; A3: FU) for the maximal work (MW) at 45°/s (continuous line) and at 10°/s (dashed line). To adhere the cross-education paradigm,[11] during the intermediate phase B the MW was assessed in each of the 16-18 training sessions in the trained limb (left panel), while a single intermediate measurement was performed, in the middle of the intervention period, in the untrained limb (right panel). Being the MW values of each subject quite different at baseline, in each graph the ordinates are enhanced to emphasize as much as possible the variations of MW throughout the entire duration of the study. Missing points during phase B indicate that subjects #1 and 4 missed the last training session. Missing points during phase A3 indicate that subject #5 missed the follow-up assessment due to drop-out.

Table 1. Demographic and clinical features of the participants at the study entry.

Demographic and Clinical outcomes	Subject No.							
	1	2	3	4	5	6	7	8
Age (years)	53	49	51	52	27	33	26	22
Gender (F/M)	M	F	F	F	M	F	F	F
MS Type	PP	RR	RR	RR	RR	RR	RR	RR
Disease duration (years)	10	1	21	13	12	8	16	11
EDSS (score)	5.5	2.0	3.5	5.0	2.0	5.5	3.0	4.5
BDI	7	10	22	5	6	2	7	7
FAB	18	14	15	15	18	17	17	16
TMT B-A (s)	100	58.7	37.7	69.8	34	24	76	48.3
Treatment	Tizanidine	Glatiramer acetate	Glatiramer acetate	Glatiramer acetate	Fingolimod	Fingolimod Baclofen	Natalizumab	Natalizumab
Walking Aids	Walking stick	None	None	None	None	AFO	None	AFO

EDSS, Expanded Disability System Status; M, Male; F, Female; MS, Multiple Sclerosis; PP, primary progressive; RR, relapsing-remitting; BDI, Beck Depression Index; FAB, Functional Assessment Battery; TMT B-A (s), Trail Making Test (seconds); AFO, Ankle Foot Orthosis.

Table 2. Reproducibility and responsiveness of maximal strength measurements from the less-affected and more-affected ankle dorsiflexion muscles at baseline over 3 time-points (test, 1-day retest; 1-week retest).

Leg	Angular velocity	Outcome measures	Relative reproducibility			Absolute reproducibility		Responsiveness	
			ICC$_{2,1}$			CV (%)		SRD	
			Session 1 vs. 2 *(95% C.I.)*	Session 1 vs. 3 *(95% C.I.)*	Session 1 vs. 2 vs. 3 *(95% C.I.)*	Session 1 vs. 2	Session 1 vs. 3	SRDi (Nm or J)	SRDi (%)
LA	10°/s	PM	0.99 *(0.96-1.00)*	0.96 *(0.83-0.99)*	0.98 *(0.80-0.90)*	5.4	9.0	2.94	9.7
		MW	0.80 *(0.21-0.96)*	0.83 *(0.30-0.97)*	0.82 *(0.49-0.96)*	14.7	12.6	1.23	14.4
	45°/s	PM	0.95 *(0.77-0.99)*	0.89 *(0.49-0.98)*	0.91 *(0.72-0.98)*	6.5	8.6	2.55	11.7
		MW	0.90 *(0.54-0.98)*	0.80 *(0.22-0.94)*	0.81 *(0.48-0.96)*	8.7	13.8	1.14	12.4
MA	10°/s	PM	0.99 *(0.96-1.00)*	0.99 *(0.98-1.00)*	0.99 *(0.99-1.00)*	1.5	1.0	1.73	7.8
		MW	0.87 *(0.43-0.98)*	0.88 *(0.48-0.98)*	0.89 *(0.67-0.98)*	13.5	12.5	1.21	17.4
	45°/s	PM	0.99 *(0.92-1.00)*	0.98 *(0.90-1.00)*	0.98 *(0.96-1.00)*	3.2	3.7	2.06	11.8
		MW	0.98 *(0.90-1.00)*	0.94 *(0.69-0.99)*	0.95 *(0.82-0.99)*	4.6	8.3	0.96	13.9

LA, less-affected limb; MA, more-affected limb; PM, Peak Moment in Newton metre; MW, maximal Work in Joule; 10°/s and 45°/s, degrees of isokinetic angular velocities; ICC, Intraclass Correlation Coefficient; C.I., Confidence Interval; CV, Coefficient of Variation; SRDi, Individual Smallest Real Difference; SRDi%, Individual Smallest Real Difference in percentage. SRDi absolute values follow the same unit of measurement of the relative outcome measure.

Table 3. Group-level assessments (*n*=7) of dynamometric outcomes at baseline (PRE), after a 3-week intervention, at the end of the 6-week intervention period and after 12 weeks from the end of the intervention.

Limb	Outcomes	PRE	INTER	POST	FU	PRE *vs* POST	POST *vs* FU	PRE *vs* FU
Less Affected Trained	PM 10°/s	30.2 (9.2) *(20.0 to 36.9)*	31.7 (8.8) *(21.9 to 37.9)*	33.8 (8.4) *(24.6 to 40.6)*	32.1 (9.3) *(21.6 to 37.2)*	+12% *(7.3 to 29.9)* $p = 0.04$	-5% *(-8.1 to -3.5)* $p = 0.02$	+6% *(1.3 to 26.5)* $p = 0.04$
	MW 10°/s	8.6 (3.0) *(5.8 to 11.4)*	9.6 (2.6) *(7.2 to 12.0)*	13.1 (2.9) *(10.4 to 15.8)*	10.2 (3.0) *(7.9 to 12.9)*	+53% *(27.3 to 64.1)* $p < 0.01$	-22% *(-27.0 to -9.8)* $p = 0.01$	+19% *(9.8 to 25.6)* $p = 0.04$
	PM 45°/s	22.1 (6.9) *(15.1 to 28.5)*	23.9 (7.2) *(17.2 to 30.6)*	26.9 (7.0) *(19.6 to 32.6)*	23.6 (7.5) *(17.3 to 29.7)*	+22% *(10.9 to 25.5)* $p = 0.03$	-12% *(-10.4 to -3.0)* $p = 0.03$	+7% *(1.8 to 19.0)* $p = 0.11$
	MW 45°/s	9.5 (3.1) *(6.6 to 12.4)*	10.4 (3.0) *(7.6 to 13.2)*	13.5 (4.0) *(9.5 to 15.9)*	10.5 (3.9) *(7.4 to 13.8)*	+42% *(15.7 to 71.5)* $p = 0.01$	-22% *(-26.2 to -12.0)* $p < 0.01$	+11% *(-7.4 to 38.8)* $p = 0.04$
More Affected Untrained	PM 10°/s	22.6 (4.4) *(18.5 to 26.7)*	23.7 (6.1) *(18.1 to 29.3)*	28.3 (7.7) *(21.2 to 35.4)*	25.1 (6.2) *(19.4 to 30.6)*	+25% *(11.0 to 36.8)* $p = 0.01$	-11% *(-15.6 to -7.4)* $p < 0.01$	+11% *(-0.7 to 14.3)* $p = 0.02$
	MW 10°/s	7.1 (2.9) *(5.4 to 9.8)*	7.4 (2.4) *(5.2 to 9.6)*	9.5 (2.9) *(6.8 to 12.2)*	8.1 (2.7) *(5.8 to 10.2)*	+33% *(-12.0 to 49.6)* $p = 0.04$	-15% *(-21.8 to -8.2)* $p = 0.01$	+13% *(-25.9 to 31.3)* $p = 0.08$
	PM 45°/s	17.9 (5.5) *(12.8 to 23.0)*	18.3 (5.7) *(13.0 to 23.6)*	22.0 (7.2) *(15.3 to 28.7)*	20.3 (7.8) *(13.7 to 26.9)*	+23% *(12.7 to 37.3)* $p = 0.01$	-8% *(-13.9 to -2.1)* $p = 0.02$	+13% *(3.2 to 23.2)* $p = 0.03$
	MW 45°/s	7.0 (2.5) *(4.7 to 9.3)*	7.1 (2.3) *(5.0 to 9.2)*	9.7 (3.2) *(6.7 to 12.7)*	7.7 (2.9) *(5.5 to 10.4)*	+39% *(14.3 to 57.9)* $p < 0.01$	-21% *(-30.6 to -4.8)* $p = 0.03$	+10% *(3.1 to 32.1)* $p = 0.09$

PM, peak moment; MW, maximal work; 45°/s, 45 degrees of angular velocity; 10°/s, 10 degrees of angular velocity. PRE: assessment at baseline; INTER, Intermediate assessment performed in a separate session after completing 3 weeks of training during the 6-week intervention period (multiple measurements carried out at each of the 16-18 training sessions for the trained limb with only one measure performed at the 9th session for the untrained limb). POST, assessment immediately after the 6-week intervention period; FU, Follow-up: assessment performed after 12 weeks from the end of intervention. Outcome values are reported as mean (SD) and 95% confidence intervals (CI). Changes in outcome values are reported as percentage values (+, increase; -, decrease) and significance of these changes are reported as *p* values, which were calculated by repeated-measures ANOVA pairwise comparisons and considered significant when < 0.05; *ns*, not significant.

Table 4. Changes and responsiveness of the clinical and functional outcomes as determined by repeated measures ANOVA ($n = 8$).

Outcomes	PRE Mean ± SD *(95% CI)*	POST Mean ± SD *(95% CI)*	FOLLOW-UP Mean ± SD *(95% CI)*	SRDi (SRDi%)	PRE *vs* POST Diff. score Unit (%)	PRE *vs* FU Diff. Score units (%)
10-MTW (s)	9.3 ± 2.6 *(7.1 to 11.5)*	8.4 ± 2.2 *(6.5 to 10.3)*	9.0 ± 2.3 *(7.0 to 11.1)*	0.72 (-7.7%)	-1.1 (-9.7%) *p = 0.029*	-0.3 (-3%) *p = 0.28*
TUG (s)	10.6 ± 2.6 *(8.4 to 12.9)*	9.4 ± 2.2 *(7.6 to 11.1)*	10.2 ± 3.2 *(8.4 to 12.2)*	1.02 (-9.6%)	-1.2 (-11.3%) *p = 0.04*	-0.4 (-3.8%) *p = 0.21*
6-MWT (m)	350.0 ± 93.0 *(272.2 to 427.7)*	378.1 ± 95.8 *(298 to 458.2)*	365.1 ± 70.5 *(301.9 to 428.0)*	n.c.	+28.1 (+8%) *p = 0.09*	+15.1 (+4.3%) *p = 0.64*

PRE: assessment at baseline; POST, assessment immediately after the 6-week intervention period; FU, Follow-up: assessment performed after 12 weeks from the end of intervention; 95% CI, 95% confidence interval; 10-MTW (s), 10-meter timed walk (seconds); TUG (s), timed up and go (seconds); 6MWT (m), 6-minute walking test (meters); n.c., not computed due to fatigue exhibited after the baseline 6MWT. Outcome values are reported as mean ± standard deviation (SD). SRD, smallest real difference. Changes in outcome values are reported as the difference score (in absolute values following the unit of measurement of each outcome), as percentage values (+, increase; -, decrease) and significance of these changes are reported as *p* values, which were calculated by repeated measures ANOVA pairwise comparisons and considered significant when < 0.05. Changes are considered meaningful when the difference score is greater than the calculated SRD value.

Table 5. Individual–level PRE to POST changes in strength of the less-affected trained ankle DF as determined by the 2 standard-deviations method.

Dynamometric	Subjects							
Outcomes	1	2	3	4	5	6	7	8#
PM 10°/s	↑*	↑*	↑	↑*	↑	↑*	↑	↑*
MW 10°/s	↑*	↑*	↑	↑*	↑*	↑*	↑*	-
PM 45°/s	↑*	↑*	↑	↑*	↑	↑	↑*	-
MW 45°/s	↑*	↑*	↑	↑*	↑	↑*	↑*	-

PM, peak moment; MW, maximal work; 10°/s, 10 degrees of angular velocity; 45°/s, 45 degrees of angular velocity. ↑*, significant improvement for at least two successive data points in the intervention phase falling outside the 2 standard-deviations band; ↑, visible trend of improvement, not statistically significant; #Subject 8, unlike the rest of the sample, underwent isometric testing, so the outcome reported is the isometric peak moment.

Table 6. Clinical relevance and responsiveness of the changes in strength after 3 and 6 weeks of resistance training and at the 12-week follow-up

ANGULAR VELOCITY		STRENGTH MEASURES	SRDi *(%)*	CHANGE (difference score)		
				PRE *vs.* INTER Unit *(%)* *(95% CI)*	PRE *vs.* POST Unit *(%)* *(95% CI)*	PRE *vs.* FUP Unit *(%)* *(95% CI)*
LA	10°/s	PM	2.94 *(9.7%)*	+1.5 *(5%)* *(-2.0 to 5.9)*	+3.6 *(12%)** *(1.0 to 6.2)*	+1.9 *(6%)* *-1.3 to 5.1)*
		MW	1.23 *(14.4%)*	+1.00 *(12%)* *(-0.9 to 2.9)*	+4.5 *(53%)** *(3.0 to 6.0)*	+1.6 *(19%)** *(-0.4 to 3.6)*
	45°/s	PM	2.55 *(11.7%)*	+1.8 *(8%)* *(-2.0 to 5.6)*	+4.8 *(22%)** *(0.7 to 8.9)*	+1.5 *(7%)* *(-2.8 to 5.8)*
		MW	1.14 *(12.4%)*	+0.9 *(9%)* *(-0.9 to 2.7)*	+4.0 *(42%)** *(1.5 to 6.5)*	+1.0 *(11%)* *(-1.0 to 3.0)*
MA	10°/s	PM	1.73 *(7.8%)*	+0.4 *(2%)* *(-2.0 to 2.8)*	+4.1 *(23%)** *(0.4 to 7.8)*	+2.4 *(13%)** *(0.4 to 4.4)*
		MW	1.21 *(17.4%)*	+0.3 *(4%)* *(-3.2 to 3.8)*	+2.4 *(33%)** *(0.3 to 4.4)*	+1.00 *(13%)* *(-1.2 to 3.2)*
	45°/s	PM	2.06 *(11.8%)*	+0.4 *(2%)* *(-1.4 to 2.2)*	+4.1 *(23%)** *(1.5 to 6.7)*	+2.4 *(13%)** *(0.1 to 4.7)*
		MW	0.96 *(13.9%)*	+0.1 *(1%)* *(-1.5 to 1.7)*	+2.7 *(39%)** *(1.2 to 4.2)*	+0.7 (10%) *(-1.6 to 2.8)*

LA, less-affected trained side; MA, more-affected untrained side; PM, Peak Moment in Newton metre; MW, Maximal Work in Joule; SRDi, Individual Smallest Real Difference as absolute and percent values; PRE, baseline assessment; INTER, intermediate assessment after 3 weeks of resistance training; POST, assessment at the end of 6-week intervention period; FUP, follow-up assessment performed after 12 weeks from the completion of the intervention. *exceeds the calculated SRDi cutoff for meaningful changes.

Table 7. Individual–level PRE to POST changes in strength of the less-affected trained and of the more-affected untrained ankle DF as determined by the smallest real difference analysis (*n*=7)*

	Assessments					
Dynamometric outcomes	PRE *vs.* INTER		PRE *vs.* POST		PRE *vs.* FU	
	LA	MA	LA	MA	LA	MA
PM 10°/s	4/7	2/7	6/7	7/7	4/6#	4/7
MW 10°/s	4/7	2/7	7/7	5/7	3/6	4/7
PM 45°/s	2/7	2/7	5/7	6/7	2/6	3/7
MW 45°/s	3/7	3/7	5/7	6/7	3/6	4/7

PM, peak moment; MW, maximal work; 10°/s, 10 degrees of angular velocity; 45°/s, 45 degrees of angular velocity. PRE, baseline assessment; INTER, intermediate assessment after 3 weeks of resistance training; POST, assessment at the end of 6-week intervention period; FUP, follow-up assessment performed after 12 weeks from the completion of the intervention. *Subject 8 was not included in the SRD analysis (see text). #Subject 5 only missed the follow-up assessment of the less-affected side.

7.8 References

1. Armstrong LE, Winant DM, Swasey PR, Seidle ME, Carter AL, Gehlsen G. Using isokinetic dynamometry to test ambulatory patients with multiple sclerosis. Phys Ther. 1983;63(8):1274-9.
2. Rice CL, Vollmer TL, Bigland-Ritchie B. Neuromuscular responses of patients with multiple sclerosis. Muscle Nerve. 1992;15(10):1123-32.
3. Ng AV, Miller RG, Gelinas D, Kent-Braun JA. Functional relationships of central and peripheral muscle alterations in multiple sclerosis. Muscle Nerve. 2004;29(6):843-52.
4. Sosnoff JJ, Socie MJ, Boes MK, Sandroff BM, Pula JH, Suh Y, Weikert M, Balantrapu S, Morrison S, Motl RW. Mobility, balance and falls in persons with multiple sclerosis. PLoS One. 2011;6(11).
5. Hayes HA, Gappmaier E, LaStayo PC. Effects of high-intensity resistance training on strength, mobility, balance, and fatigue in individuals with multiple sclerosis: a randomized controlled trial. J Neurol Phys Ther. 2011;35(1):2-10.
6. Kjølhede T, Vissing K, Dalgas U. Multiple sclerosis and progressive resistance training: a systematic review. Mult Scler. 2012;18(9):1215-28.
7. Dalgas U, Stenager E, Jakobsen J, Petersen T, Hansen HJ, Knudsen C, Overgaard K, Ingemann-Hansen T. Fatigue, mood and quality of life improve in MS patients after progressive resistance training. Mult Scler. 2010;16(4):480-90.
8. Rietberg MB, van Wegen EE, Uitdehaag BM, Kwakkel G. The association between perceived fatigue and actual level of physical activity in multiple sclerosis. Mult Scler. 2011;17(10):1231-7.
9. Carroll TJ, Herbert RD, Munn J, Lee M, Gandevia SC. Contralateral effects of unilateral strength training: evidence and possible mechanisms. J Appl Physiol (1985). 2006;101(5):1514-22.
10. Zhou S. Chronic neural adaptations to unilateral exercise: mechanisms of cross education. Exerc Sport Sci Rev. 2000;28(4):177-84.

11. Munn J, Herbert RD, Gandevia SC. Contralateral effects of unilateral resistance training: a meta-analysis. J Appl Physiol (1985). 2004;96(5):1861-6.
12. Manca A, Pisanu F, Ortu E, De Natale ER, Ginatempo F, Dragone D, Tolu E & Deriu F. A comprehensive assessment of the Cross-training effect in ankle dorsiflexors of healthy subjects: a randomized controlled study. Gait & Posture. 2015*a*; DOI: 10.1016/j.gaitpost.2015.04.005.
13. Magnus CR, Arnold CM, Johnston G, Dal-Bello Haas V, Basran J, Krentz JR, Farthing JP. Cross-education for improving strength and mobility after distal radius fractures: a randomized controlled trial. Arch Phys Med Rehabil. 2013;94(7):1247-55.
14. Farthing JP, Borowsky R, Chilibeck PD, Binsted G, Sarty GE. Neuro-physiological adaptations associated with cross-education of strength. Brain Topogr. 2007;20(2):77-88.
15. Dragert K, Zehr EP. High-intensity unilateral dorsiflexor resistance training results in bilateral neuromuscular plasticity after stroke. Exp Brain Res. 2013;225(1):93-104.
16. Urbin MA, Harris-Love ML, Carter AR, Lang CE. High-Intensity, Unilateral Resistance Training of a Non-Paretic Muscle Group Increases Active Range of Motion in a Severely Paretic Upper Extremity Muscle Group after Stroke. Front Neurol. 2015 May 27;6:119.
17. Manca A, Ortu E, De Natale ER, Ginatempo F, Dragone D, Tranquilli Leali PT, Deriu F. Isokinetic cross-training effect in foot drop following common peroneal nerve injury. Isokinet Exerc Sci. 2015*b*;23:17-20. DOI: 10.3233/IES-140559.
18. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69(2):292-302.

19. Backman CL, Harris SR. Case studies, single-subject research, and N of 1 randomized trials: comparisons and contrasts. Am J Phys Med Rehabil. 1999;78(2):170-6.
20. Bäckman E, Oberg B. Isokinetic muscle torque in the dorsiflexors of the ankle in children 6-15 years of age. Normal values and evaluation of the method. Scand J Rehabil Med. 1989;21(2):97-103.
21. Goldman MD, Marrie RA, Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. Mult Scler. 2008;14(3):383-90.
22. Paltamaa J, West H, Sarasoja T, Wikström J, Mälkiä E. Reliability of physical functioning measures in ambulatory subjects with MS. Physiother Res Int. 2005;10(2):93-109.
23. 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.
24. Moritani T, deVries HA. Neural factors versus hypertrophy in the time course of muscle strength gain. Am J Phys Med. 1979; 58: 115-130.
25. Enoka RM. Neural adaptations with chronic physical activity. J Biomech. 1997; 30: 447-455.
26. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull. 1979;86(2):420-8.
27. Lexell Lexell JE, Downham DY. How to assess the reliability of measurements in rehabilitation. Am J Phys Med Rehabil. 2005;84(9):719-723.
28. Dvir Z. Difference, significant difference and clinically meaningful difference: The meaning of change in rehabilitation. J Exerc Rehabil. 2015 Apr 30;11(2):67-73.
29. Harbo Harbo T, Brincks J, Andersen H. Maximal isokinetic and isometric muscle strength of major muscle groups related to age, body mass, height, and sex in 178 healthy subjects. Eur J Appl Physiol. 2012;112(1):267-275.
30. Manca A, Solinas G, Dragone D, Dvir Z, Deriu F. Characterization of ankle dorsiflexors performance in healthy subjects following maximal-intensity isokinetic

resistance training. J Electromyogr Kinesiol. Epub ahead of print 17 Jun 2015. doi: 10.1016/ j.jelekin.2015.06.002.

31. Manca A, Pisanu F, Ortu E, De Natale ER, Ginatempo F, Dragone D, Tolu E, Deriu F. A comprehensive assessment of the cross-training effect in ankle dorsiflexors of healthy subjects: A randomized controlled study. Gait Posture. 2015 Jun;42(1):1-6.
32. Davies, GJ. A Compendium of Isokinetics in Clinical Usage and Rehabilitation Techniques. 4th Ed. Onalaska, WI: S. & S Publishers; 1992.
33. Dvir Z, David G. Average or peak moment: Which of the two is more suitable to represent isokinetic muscle strength? Isokinetics Exerc Sci. 1995;5(2):93-7.
34. Broekmans T, Roelants M, Feys P, Alders G, Gijbels D, Hanssen I, Stinissen P, Eijnde BO. Effects of long-term resistance training and simultaneous electro-stimulation on muscle strength and functional mobility in multiple sclerosis. Mult Scler. 2011;17(4):468-77.
35. Hunter SM, Crome P, Sim J, Pomeroy VM. Effects of mobilization and tactile stimulation on recovery of the hemiplegic upper limb: a series of replicated single-system studies. Arch Phys Med Rehabil. 2008;89(10):2003-10.
36. Riddoch J, Lennon S. Single Subject Experimental Design: One Way Forward? Physiother. 1994;80(4):215-18.
37. Bloom M, Fischer J, Orme JG. Evaluating Practice: Guidelines for the Accountable Professional. 6th Edition ed. Boston: Allyn and Bacon; 2009.

Summary of the main findings

Characterization of muscle performance in healthy subjects

Contrary to what was previously described in the literature, muscle performance in healthy individuals can be described not only in terms of the conventional peak of maximum force (in Newtons meters) but also as muscle work (in joules), a parameter that describes more appropriately the functional capacity of a muscle group and whose changes can have major clinical implications in patients functional.

Characterization of muscular performance in individuals with multiple sclerosis

Compared with healthy subjects, patients with relapsing remitting multiple sclerosis with a mild to moderate disability have a similar peak force (in Newton meters) but are significantly less capable of producing muscle work (in joules). This has a negative impact on muscle performance since patients experience difficulties in maintaining adequate strength levels over distance and over time.

Study of the reproducibility, reliability and responsiveness of measurements of muscle strength in healthy subjects and in patients with neurological diseases

Through indices of reproducibility such as the of intraclass correlation (ICC), the standard error of measurement (SEM) and the coefficient of variation (CV%) it was possible to highlight the differences between healthy subjects and patients with multiple sclerosis in terms of reliability and precision of the measurements of maximal strength. The novel finding of this study is that, even in patients with multiple sclerosis, who are generally considered highly unstable in their capacity to produce strength against a resistance, measurements of maximum strength are highly stable and reproducible.

Assessment of strength by peak force and maximal work capacity in healthy subjects

Employing a protocol of muscle strengthening at high intensity allows the improvement of both the peak force (in newton meters) and muscle work capacity (in joules). In particular, this performance parameter is likely to be more responsive *than peak force since maximal work values after training are found to be changed to a greater extent than peak force.*

Evaluation of the dynamometric and clinical-functional effects of resistance training delivered at maximal intensity in patients with multiple sclerosis

Contrary to what was previously described in the literature devoted, the use of the maximality of training in MS patients may represent a new approach in the treatment of muscle weakness as the results obtained from patients with relapsing-remitting MS and disability mild to moderate respond so comparable with healthy subjects matched for age and anthropometric characteristics.

Study of the Cross-training phenomenon in healthy subjects and its neurorehabilitative implications

It is now accepted that training one limb can result into the indirect improvement of performance in the contralateral untrained side. Basing on these premises, this study was aimed at collecting data on this phenomenon in the ankle dorsiflexion muscles for two main reasons: 1) the ankle dorsiflexors are frequently involved in neurological conditions and their impairment affects the physiological gait; 2) the cross-training phenomenon had never been studied before in the dorsiflexion muscles of healthy individuals neither in individuals suffering from neurological or orthopaedic conditions. Among the study findings, it has been demonstrated a magnitude of transfer greater than that previously described in previous literature on other muscle groups. This can be explained by the different training protocol adopted and by the maximal intensity employed in the training, compared to submaximal protocols conventionally used in research and rehabilitation.

Study of the effects of contralateral training in patients with multiple sclerosis

The Cross-training phenomenon also occurred in patients with demyelinating disease and with a magnitude of effect that is similar to that described in healthy subjects. Based on the data collected, it is conceivable to hypothesize a direct relationship between the level of disability and the amount of transfer observed, which, however, deserves to be confirmed and further investigated in a larger population.

Study of the time-course and dose-response relationships of the strength adaptations to resistance training in patients with multiple sclerosis

Direct resistance training at a maximal intensity in patients with multiple sclerosis induces substantial and statistically significant improvements after only three weeks (in healthy this occurs between the 4th and the 5th week of training). After the 3rd week patients exhibit a stable plateau in performance that is not likely to improve grow in the remaining weeks of training. Fatigue and disability reported by patients with multiple sclerosis may play a prominent role in the exhibited temporal responses to training. The results from a cohort of 25 patients with relapsing remittent multiple sclerosis need to be confirmed on a larger sample but, still, raise interesting questions on the proper amount of exercise rehabilitation to be prescribed, with potential implications for clinical practice and health economics.

Comparative study of effectiveness between direct and indirect training in multiple sclerosis

This study exploratory study aimed at comparing the direct training which is conventionally employed in neurorehabilitation to contralateral training (Cross-training) in the management of unilateral muscle weakness in patients with relapsing-remittent multiple sclerosis. Data from 30 patients randomized into two groups of equal size revealed an unexpected superiority of the indirect versus direct training approach. In the group trained with the Cross-training, patients showed a linear increase of muscle strength over time, unlike the group undergoing direct training which, after 3 weeks, showed a plateau or a deflection of the strength levels, likely due to the onset of fatigue within the most-affected limb when maximally exercised. No substantial differences in strength, however, were detected between the two groups after a period of follow-up of 3 months.

Final perspectives and conclusions

Based on the data collected in the framework of the present project which was primarily aimed at translating sports physiology knowledge into the neurological paradigm, it can be legitimately concluded that such approach is promising and deserves further attention and well-planned statistically powered research. Compared to the conventional quite cautious but somehow restrained management of individuals with neurological conditions, assessing and training muscle strength through evidence-based sports-derived methods is likely to induce greater gains in performance and, consequently, in the functional capacity, resulting into enhanced activities of the daily living and independence.

We believe that such approach should be taken into proper consideration when planning interventions to address muscle weakness in neurological patients. Whether translational rehabilitation effectively applies to other disabilities such as fatigue and balance impairment will be the next step of the present research line.