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ORIGINAL ARTICLE

WILEY

Training load but not fatigue affects cross-education of maximal voluntary force

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The purpose of this study was to determine the effects of training load (25% vs. 75% of one repetition maximum [1RM]) and fatigue (failure vs. non-failure) during four weeks of unilateral knee extension resistance training (RT) on maximal voluntary force in the trained and the untrained knee extensors. Healthy young adults ($n = 42$) were randomly assigned to control (CON, $n = 9$, 24 ± 4.3 years), low-load RT to failure (LLF, $n = 11$, 21 ± 1.3 years, three sets to failure at 25% of 1RM), high-load RT to failure (HLF, $n = 11$, 21 ± 1.4 years, three sets to failure at 75% of 1RM), and high-load RT without failure (HLNF, $n = 11$, 22 ± 1.5 years, six sets of five repetitions at 75% of 1RM) groups. Before and after the four weeks of training, 1RM, maximal voluntary isometric force, and corticospinal excitability (CSE) were measured. 1RM in the trained (20%, $d = 0.70$, 15%, $d = 0.61$) and the untrained knee extensors (5%, $d = 0.27$, 6%, $d = 0.26$) increased only in the HLF and HLNF groups, respectively. MVIC force increased only in the trained leg of the HLF (5%, $d = 0.35$) and HLNF groups (12%, $d = 0.67$). CSE decreased in the VL of both legs in the HLNF group (−19%, $d = 0.44$) and no changes occurred in the RF. In conclusion, high- but not low-load RT improves maximal voluntary force in the trained and the untrained knee extensors and fatigue did not further enhance these adaptations. Voluntary force improvements were unrelated to CSE changes in both legs.

KEYWORDS
corticospinal excitability, interlimb transfer, knee extensors, resistance training

1 | INTRODUCTION

Voluntary force is a determinant of sport performance, closely related to the risk of falls in older adults and is also a strong predictor of mortality and hospitalization.[1] Therefore, it is important to determine the resistance training (RT) protocol that is most efficacious in increasing maximal voluntary force. A number of variables can be manipulated during RT such as load[2] or volume,[3] to maximize RT-induced increases in maximal voluntary force. For example, some evidence suggests that heavy compared with light loads, even at the same total volume and all the sets performed to concentric muscular failure, are more effective in increasing maximal voluntary force.[2] Another factor contributing to the adaptive responses to RT is fatigue that develops during the exercise bout or set, which could be manipulated through the modification of training variables like volume or load. Some studies suggest that training to concentric muscular failure, that is, the inability to perform one further concentric repetition, could enhance RT adaptations[4] by increasing metabolic stress and motor unit activation.[5] However, there is also evidence suggesting that muscle failure during training may not be necessary to increase maximal voluntary force.[6]

Unilateral RT can also increase maximal voluntary force in the untrained limb, producing cross-education (CE).[7] However, unlike in the trained limb, how load or fatigue developed during the sets affect CE is unclear.[8] Because CE can occur without muscle hypertrophy, it is generally accepted that neural mechanisms underlie CE.[7,9,10] Specifically, it is believed that CE arises from neural adaptations in the untrained hemisphere, induced by the simultaneous but lower activation of this hemisphere along with the active hemisphere during forceful unilateral contractions.[7] The characteristics of the unilateral contraction affect the concurrent ipsilateral hemisphere activation. For example, the size of the responses to transcranial magnetic stimulation (TMS) of the resting hemisphere during unilateral contractions increases with contraction intensity.[11,12] Because this modulation does not occur in the responses to cervicomedullar electrical stimulation of the corticospinal axons,[12] the data suggest that the facilitation of the motor-evoked potentials (MEP) in the contralateral homologous muscles occurs because of a concomitant increase in the excitability of the resting motor cortex. In addition, imaging data suggest that the concurrent activation of the sensorimotor cortex of the ipsilateral hemisphere also increases when a unilateral isometric contraction is produced at a low intensity but for a prolonged period of time,[13] suggesting that the concurrent activation of the ipsilateral hemisphere increases with the evolution of fatigue. Therefore, the magnitude of the load or fatigue during the RT set could affect the magnitude of CE through their influence on the concurrent ipsilateral hemisphere activation,[8] as occur with other training variables like the type of muscle contraction. For example, eccentric, compared with concentric or isometric contractions, is associated with heightened activation of the ipsilateral hemisphere,[14] resulting in greater CE of voluntary force.[15]

However, most studies examining RT-induced CE used training loads >50% of MVIC or 1RM[9,10,16-19] and the few studies using low-load RT reported inconsistent results,[20,21] as low-load RT for 3-4 weeks with or without blood flow restriction produced either 26%[20] or no CE,[21] respectively. Differences could be related to blood flow restriction increasing fatigue in the trained leg, which in turn increases activation in the ipsilateral hemisphere and subsequent CE. This theory is supported by a recent study showing that CE was higher after five weeks of elbow flexors training using a traditional set configuration (5 × 6 with a 10 repetition maximum load) compared with a cluster training set configuration (30 repetitions with 18.5 seconds of rest between each rep),[22] suggesting a role of fatigue in CE.

It thus appears reasonable to hypothesize that high loads and fatigue, respectively, during the RT set could facilitate CE. This is because RT with high loads and/or high levels of fatigue would strongly activate the ipsilateral motor areas in the brain, acting as a training stimulus for the untrained limb. Therefore, the purpose of the present study was to determine the effects of training load (25% vs 75% of one repetition maximum [1RM]) and fatigue (failure vs non-failure) during unilateral RT on maximal voluntary force increases in the untrained knee extensors (ie, CE) in healthy untrained males after four weeks of unilateral RT. In addition, we also examined the effect of training load and fatigue on the maximal voluntary force adaptations of the trained limb, and the potential neural correlates underlying these adaptations in both limbs in the form of corticospinal excitability (CSE) using TMS.

A detailed understanding of how load and fatigue affect adaptations to RT in the untrained limb is relevant for the rehabilitation of patients with weakness in one limb that cannot train bilaterally.

2 | MATERIAL AND METHODS

2.1 | Participants

Healthy, recreationally active men (n = 42, 21.8 ± 2.4 years, 6 left-legged) without experience in RT and lower limb injury history, volunteered for the study. Recreational activities included 2-3 h/wk of sports (mostly team sports) or aerobic training. Participants reported no contraindications to TMS and were not currently taking any medications. Participants gave written informed consent for the experimental procedures approved by the Institutional Review Board of the Catholic University of Murcia. The study was performed in accordance with the latest Declaration of Helsinki. Participants visited the laboratory one week prior to the beginning of the experiment for familiarization with the testing procedure. Participants were asked to refrain from consuming alcohol, caffeine, and from exercising at least 48 hours before each testing session. During the experiment, participants were reminded to keep their daily habits and not take nutritional supplements or start new training programs.

2.2 | Study design and training

Figure 1 shows the design. All participants came to the laboratory three times before the start of RT. One session was for familiarization and two additional identical sessions were for pre-test sessions (PRE-1, PRE-2). Sessions were separated by one week of rest. After 4 weeks of RT, participants came to the laboratory for the final post-test (POST, 96-120 hours after last training session). Each testing session started with maximal voluntary isometric contractions (MVIC), followed

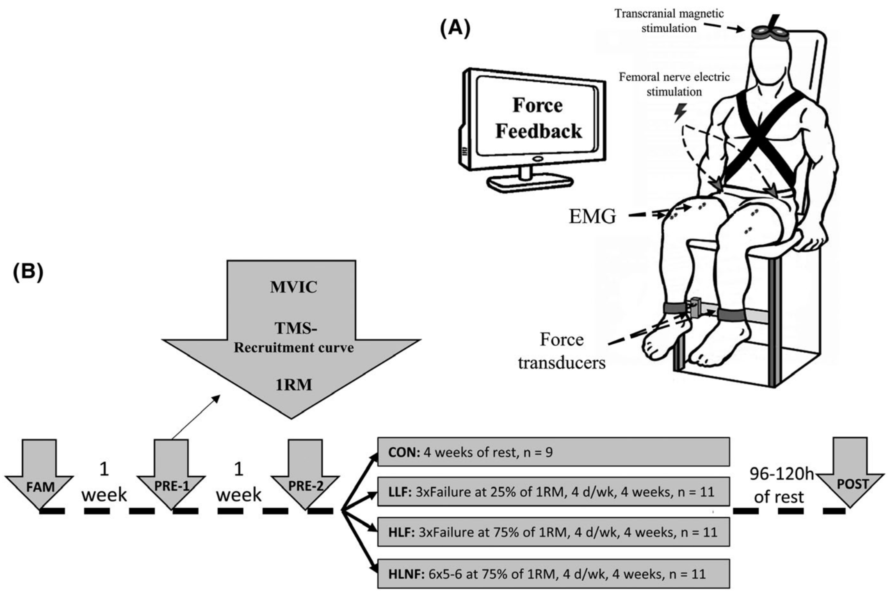

FIGURE 1 Schematic view of the set-up and protocol. A, Participants sat in a custom-made chair with the hip, knee, and ankle at 90° and the torso restrained with belts to avoid displacement during isometric contractions. B, Schematic representation of the experimental design

by measurements of CSE and ended with 1RM testing of the knee extensors of each leg separately.

After the pre-test sessions, participants were randomly assigned to four groups: control (CON, n = 9, 23.5 ± 4.3 years), low-load RT to concentric muscular failure (LLF, n = 11, 20.8 ± 1.3 years), high-load RT to concentric muscular failure (HLF, n = 11, 21.4 ± 1.4 years), and high-load RT without failure (HLNF, n = 11, 21.8 ± 1.5 years). CON continued with their daily habits during 4 weeks between PRE-2 and POST. The participants in the training groups performed unilateral knee extension RT with the dominant leg, which was self-reported, four times per week for four weeks (Monday, Tuesday, Thursday, Friday). We chose a high frequency RT (4 days per week) to increase the total number of training sessions based on a previous study showing that minimizing rest days between training sessions during short RT periods may improve CE when increases in voluntary force of the trained limb are not the main focus.[23]

Before each training session, participants performed a short warm-up consisting of 10 repetitions with a load of 25% of 1RM. Training in the LLF and HLF groups consisted of three sets of unilateral dominant knee extensions to concentric muscular failure with a load corresponding to the 25% and 75% of 1RM, respectively. Concentric muscular failure was defined as the moment when participants were unable to complete one additional repetition through the full range of motion. The HLNF group trained with a load corresponding to the 75% of 1RM but without reaching concentric muscular failure. Because a 75% of 1RM corresponds to a load that could be lifted ~10 times (ie, 10RM), participants in the HLNF group performed six sets of five repetitions, half of the maximal number of repetitions that could be done with that load. Therefore, to equate the volume between HLF and HLNF, the HLNF group performed six sets instead of three. Load was maintained constant during the 4 weeks. Because the number of repetitions of the HLF group increased across the training sessions, the number of repetitions in each set in the HLNF group increased from 5 to 6 after the 2nd week to maintain similar volumes. Participants performed each knee extension as fast as possible in the concentric phase and controlled eccentric phase supervised by the investigators with an inter-set rest period of 2 minutes. The only instruction given related to the non-training leg was not to push with the leg against the load, but participants were not instructed explicitly to relax this leg. After each set, the number of repetitions completed and the ratings of perceived exertion (RPE) was registered using the OMNI-RES scale (0-10), where 0 is extremely easy and 10 represents an extremely hard effort.[24] Participants were familiarized with the OMNI-RES scale before the initiation of the study. The daily average number of repetitions, volume (reps*Kg) and RPE was calculated for each group.

2.3 | Set-up

Participants sat in a custom-made chair with the hip, knee, and ankle at 90°, and the torso restrained with belts to avoid displacement (Figure 1A). Both legs were fastened with two rigid straps around the ankle to two force transducers (NL63, 200 kg; Digitimer, Welwyn Garden City, UK) to measure voluntary force (band-pass-filtered 5-2,500Hz, amplified ×1000 and sampled at 2 kHz).

Surface electromyography (EMG) was recorded from the right and left vastus lateralis (VL) and rectus femoris (RF) using Ag-AgCl surface electrodes (2 cm interelectrode distance) attached to the skin according to SENIAM recommendations. EMG signals were amplified (×600-1000 depending on the baseline $M_{\max}$ amplitude at PRE-1), band-pass-filtered (10-500 Hz), and sampled (2 kHz) with a Digitimer d440-isolated amplifier (Digitimer). EMG and force recordings were simultaneously collected using an analog-digital board CED Micro 1401-3 (Cambridge Electronic Design) for further analysis.

2.4 | Maximal voluntary force tests

At the beginning of the testing sessions, in the position described above (Figure 1A), participants performed two unilateral 3-5 seconds MVIC with each leg. In each trial, participants contracted as hard and fast as possible. MVIC measurements started always with the dominant leg and every attempt was performed one minute after the trial of the other leg so participants rested around two minutes between trials of the same leg. The mean peak-to-peak value of the two attempts of each leg was used to determine the target force for submaximal torque contraction during the CSE measurements. The maximal EMG_{RMS} of the VL (VL-$\text{EMG}_{\text{RMSmax}}$) and the RF (RF-$\text{EMG}_{\text{RMSmax}}$) was computed offline in a time window of 500 ms around the peak force and normalized to the amplitude of the M_{max}.

Maximal unilateral voluntary dynamic force of the knee extensors was measured using a standard unilateral 1RM test in a commercial seated knee extension machine (Technogym). Before the first attempt, every participant performed a warm-up consisting on ten, eight, four, and two repetitions with a load equivalent to the 20, 40, 60, and 80% of their estimated 1RM, respectively. After warming up, participants performed trials of one repetition with increasing loads (~10%-20% steps) until they were not able to complete one repetition through the full range of motion (from 90° to 180° of extension). Three minutes of rest were given between trials, and the entire protocol was performed with the dominant and non-dominant leg, in that order. A single set to failure was done with the dominant limb to test the maximal number of repetitions with the 75% of 1RM in PRE-2. Verbal encouragement was given in each attempt of maximal dynamic voluntary force. The highest load lifted in each session was used as the 1RM. The mean CE effect for MVC and 1RM in the training groups was estimated by subtracting the mean change in the force of the untrained leg in the CON group from the mean change in force in the training groups.[25]

2.5 | Transcranial magnetic stimulation

Single-pulse TMS was delivered to the left and right motor cortices using a concave double-cone coil (120 mm) which induced a posterior-anterior intracranial current connected to a DuoMag (Rogue Resolutions Ltd) magnetic stimulator. The optimal stimulation point of each leg was obtained by exploring the estimated center of the quadriceps muscles cortical representation. The point at which MEP were the largest in each session was marked on the scalp with a permanent marker. Active motor threshold (AMT) for each leg was determined as the lowest stimulation intensity that produced three out of five MEPs of a peak-to-peak amplitude >200 μV during a 5% unilateral MVIC whereby MVIC force was displayed as a line in a monitor in front of the participant.

To measure CSE, a recruitment curve (RC) was measured in both legs during a unilateral contraction at 5% of the MVIC force. Stimulation intensity started with a subthreshold intensity of 30% of the stimulator output and increased in steps of 10% until 90% of the stimulator output. Four pulses were given at each stimulation intensity. The peak-to-peak amplitude of MEPs obtained in the VL and RF of each leg was measured offline and used to calculate the total area under the recruitment curve (AURC) using the trapezoidal integration method. The root mean square of the EMG (EMG_{RMS}) during the 150 ms previous to the pulse was also measured and averaged for each session.

2.6 | Peripheral nerve stimulation

The maximal compound muscle action potential (M_{max}) of both legs was obtained via single-pulse electrical stimulation (200 μs duration) delivered to the femoral nerve with a DS7AH constant current electrical stimulator (Digitimer). The cathode (pregelled Ag-AgCl electrodes) was located over the femoral triangle and the anode midway between the greater trochanter and the iliac crest. The intensity for stimulation was set at 120% of the stimulation intensity needed to elicit a maximum VL and RF-M_{max}. Five pulses were obtained in each leg at the beginning of each session during a contraction of 5% of MVIC force. The peak-to-peak amplitude of the M_{max} and the associated twitches (Tw-M_{max}) were measured and averaged. The average M_{max} value of each testing session was then used for normalization procedures of all the other EMG variables.

2.7 | Statistics

All variables were normally distributed and the variances were homogeneous according to the Kolmogorov-Smirnov test and Levene tests, respectively. Intersession reliability of measurements obtained in PRE-1 and PRE-2 was determined using intraclass correlation coefficients (ICC (2, 1) two-way mixed effect model) with 95% confidence intervals. To determine baseline differences between PRE-1 and PRE-2, paired t test analysis was performed for all variables (See Table S1 in supporting information) and the mean value of PRE-1 and PRE-2 was used for subsequent analysis (PRE). A one-way ANOVA with group (LLF, HLF, HLNF) as factor was performed for the training variables (REPs/day, VOL/day, and RPE/day). A three-way

TABLE 1 PRE-POST mean raw values and Cohen's d effect size for each group and variable

	PRE	POST	*d*		PRE	POST	*d*
Trained				*Untrained*			
1RM (kg)				1RM (kg)			
CON	56.44 ± 6.71	57.33 ± 6.71	0.01	CON	59.22 ± 6.06	59.33 ± 8.66	0.01
LLF	57.19 ± 10.28	58.27 ± 13.42	0.09	LLF	59.18 ± 8.83	59.54 ± 9.68	0.01
HLF	58.09 ± 12.86	69.73 ± 19.76	0.70	HLF	59.18 ± 10.49	62.18 ± 11.43	0.27
HLNF	58.18 ± 12.53	66.64 ± 15.17	0.61	HLNF	59.18 ± 14.47	63.00 ± 14.72	0.26
MVIC (N)				MVIC (N)			
CON	618.21 ± 64.27	624.33 ± 79.28	0.08	CON	628.78 ± 82.01	632.81 ± 96.97	0.04
LLF	586.06 ± 110.81	570.32 ± 118.94	0.14	LLF	589.39 ± 104.76	590.75 ± 107.17	0.01
HLF	615.06 ± 99.40	650.98 ± 103.05	0.35	HLF	593.26 ± 90.32	595.31 ± 85.97	0.02
HLNF	580.88 ± 103.21	651.77 ± 107.01	0.67	HLNF	574.22 ± 120.73	595.74 ± 121.31	0.18
VL-EMG$_{RMS}$ (%M$_{max}$)				VL-EMG$_{RMS}$ (%M$_{max}$)			
CON	0.075 ± 0.020	0.075 ± 0.026	0.01	CON	0.074 ± 0.016	0.076 ± 0.024	0.07
LLF	0.087 ± 0.026	0.084 ± 0.035	0.09	LLF	0.078 ± 0.034	0.068 ± 0.036	0.28
HLF	0.084 ± 0.030	0.094 ± 0.040	0.30	HLF	0.077 ± 0.033	0.072 ± 0.026	0.17
HLNF	0.101 ± 0.046	0.107 ± 0.052	0.12	HLNF	0.083 ± 0.026	0.093 ± 0.039	0.29
VL-EMG$_{RMS}$ (%M$_{max}$)				VL-EMG$_{RMS}$ (%M$_{max}$)			
CON	0.084 ± 0.029	0.097 ± 0.031	0.43	CON	0.113 ± 0.039	0.102 ± 0.026	0.32
LLF	0.106 ± 0.043	0.120 ± 0.039	0.34	LLF	0.111 ± 0.036	0.110 ± 0.035	0.04
HLF	0.118 ± 0.044	0.133 ± 0.046	0.33	HLF	0.103 ± 0.037	0.098 ± 0.024	0.15
HLNF	0.119 ± 0.049	0.135 ± 0.054	0.32	HLNF	0.106 ± 0.052	0.100 ± 0.030	0.14
VL-AURC (a.u)				VL-AURC (a.u)			
CON	86.84 ± 62.86	102.58 ± 63.23	0.25	CON	75.41 ± 29.04	87.65 ± 46.78	0.31
LLF	89.38 ± 65.70	71.58 ± 46.21	0.31	LLF	99.75 ± 61.63	91.49 ± 53.90	0.14
HLF	89.70 ± 48.05	80.88 ± 54.97	0.17	HLF	104.57 ± 50.55	93.05 ± 47.78	0.23
HLNF	115.33 ± 54.77	89.69 ± 63.69	0.43	HLNF	118.09 ± 40.84	100.49 ± 35.22	0.46
RF-AURC (a.u)				RF-AURC (a.u)			
CON	156.63 ± 68.50	162.55 ± 75.57	0.08	CON	151.07 ± 58.77	149.29 ± 48.77	0.03
LLF	209.41 ± 117.86	171.83 ± 99.93	0.34	LLF	160.21 ± 81.87	151.18 ± 73.85	0.11
HLF	114.28 ± 68.72	102.63 ± 78.85	0.16	HLF	164.28 ± 75.58	164.00 ± 82.01	0.01
HLNF	168.55 ± 86.74	137.91 ± 66.90	0.39	HLNF	166.71 ± 54.80	151.75 ± 62.34	0.25
AMT (%MSO)				AMT (%MSO)			
CON	43.28 ± 5.18	44.44 ± 4.61	0.24	CON	43.44 ± 6.17	44.33 ± 7.24	0.13
LLF	44.78 ± 6.73	43.36 ± 7.96	0.19	LLF	41.86 ± 4.15	41.55 ± 3.78	0.08
HLF	48.64 ± 10.52	47.73 ± 10.14	0.09	HLF	45.73 ± 7.13	46.46 ± 7.66	0.10
HLNF	42.55 ± 7.27	44.09 ± 8.34	0.20	HLNF	41.41 ± 7.04	41.18 ± 7.05	0.03
VL-M$_{max}$ (mV)				VL-M$_{max}$ (mV)			
CON	5.30 ± 0.67	4.70 ± 2.01	0.40	CON	4.63 ± 1.66	4.34 ± 1.31	0.19
LLF	5.28 ± 1.69	5.67 ± 1.59	0.23	LLF	5.50 ± 1.98	5.47 ± 1.46	0.02
HLF	4.37 ± 1.40	5.18 ± 3.30	0.32	HLF	5.24 ± 1.98	5.37 ± 2.46	0.06
HLNF	4.92 ± 1.74	5.21 ± 1.47	0.17	HLNF	5.13 ± 1.91	5.28 ± 1.80	0.08
RF-M$_{max}$ (mV)				RF-M$_{max}$ (mV)			
CON	4.54 ± 1.32	3.57 ± 1.88	0.59	CON	3.11 ± 1.02	3.20 ± 0.91	0.09
LLF	3.47 ± 1.35	3.67 ± 1.47	0.14	LLF	3.12 ± 1.08	3.78 ± 2.11	0.39

(Continues)

TABLE 1 (Continued)

	PRE	POST	*d*		PRE	POST	*d*
HLF	3.41 ± 1.14	4.01 ± 1.14	0.52	HLF	3.73 ± 1.11	3.96 ± 0.88	0.23
HLNF	3.94 ± 1.55	3.98 ± 1.59	0.02	HLNF	3.36 ± 0.98	3.60 ± 1.30	0.21
Tw-M_{max} (N)				Tw-M_{max} (N)			
CON	92.92 ± 23.48	90.99 ± 29.85	0.07	CON	99.60 ± 26.92	99.97 ± 27.85	0.01
LL	96.71 ± 23.94	77.88 ± 26.88	0.74	LL	107.38 ± 20.88	105.72 ± 24.34	0.07
HLF	92.29 ± 27.24	82.86 ± 28.62	0.34	HLF	98.53 ± 29.00	96.76 ± 23.46	0.07
HLNF	93.53 ± 24.81	93.04 ± 24.85	0.02	HLNF	100.47 ± 18.34	96.44 ± 28.20	0.17

Abbreviations: 1RM: one repetition maximum; AURC: area under the curve; d: Cohen's *d* effect size; EMG_{RMS}, maximum electromyography root mean square; MEP, Motor-evoked potential; M_{max}, Maximal compound muscle action potential.; MVIC, maximum voluntary isometric contraction; RF, rectus femoris; VL, vastus lateralis.

repeated measures analysis of variance (RM-ANOVA) was performed with time (PRE and POST), leg (trained and untrained), and group (CON, LL, HLF, HLNF) as factors for the following variables: 1RM, MVIC force, VL-EMG_{RMS}, RF-EMG_{RMS}, VL-AURC, RF-AURC, AMT, VL and RF-M_{max} and Tw-M_{max}. When significant interactions or main effects were found, Bonferroni correction was applied to account for multiple comparisons in the post-hoc analyses. A post-hoc power and a sensitivity analysis were performed by using the G*Power software (version 3.1.9.2, Heinrich Heine University). The statistical power for the within-between interaction in a repeated measures ANOVA, an alpha level of .05, a total sample size of 42, 4 groups, 2 measurements, a correlation among repeated measures of 0.5, and a medium effect size (f = 0.25) is 0.75 (ie, 75%). Additionally, the sensitivity of the tests for an alpha level of 0.05 and a power of 0.80 was sufficient for detecting a medium effect size f = 0.27 for the interaction. ES are presented as partial eta-squared values (η_p^2; small: 0.01; medium: 0.06; large: 0.14; see Table S2 in supporting information) for the factors of the RM-ANOVAs and as Cohen's *d* for the paired comparisons (See Table S1 in supporting information and Table 1 and results section). When needed, correlations were determined by using Pearson correlation analysis. Data are presented as mean ± standard deviation (SD) in the text and figures. SPSS 20.0 software (SPSS) was used for statistical analysis. Statistical significance was set at $P \leq .05$.

3 | RESULTS

3.1 | Reliability

Intersession reliability ranged from 0.65 to 0.96 for all variables (See Table S1 in supporting information). There were no significant baseline differences between PRE-1 and PRE-2 for all variables except for Tw-M_{max} (see Table S1 in supporting information).

3.2 | Training variables

The mean number of repetitions done at 75% of 1RM before training was 9.3 ± 3.2. The daily number of repetitions was higher in LLF (117 ± 17 reps/day) compared with HLF (34 ± 3 reps/day, *d* = 6.9, *P* = .001) and HLNF (33 ± 0.8 reps/day, *d* = 7.0, *P* = .001) without differences between the HLF and HLNF (*d* = 0.1, *P* = .99). However, the total volume was not different between LLF (1877 ± 533 kg/d), HLF (1504 ± 335 kg/d, *d* = 0.84, *P* = .112), and HLNF (1470 ± 297 kg/d, *d* = 0.94, *P* = .072) or between HLF and HLNF (*d* = 0.1, *P* = .99). The groups training to failure reported a higher RPE (LLF: 9.5 ± 0.5, HLF: 9.6 ± 0.4) than HLNF (6.2 ± 0.7, *d* = 5.14 and 5.81, respectively, both *P* = .001).

3.3 | Voluntary dynamic force (1RM)

Before training, 1RM values were similar between groups in each leg (all *P* > .05). After four weeks of RT, 1RM of the trained leg increased in HLF (20%, *d* = 0.70, *P* = .001) and HLNF (15%, *d* = 0.61, *P* = .001) but not in LLF (2%, *d* = 0.09, *P* = .59) or CON (2%, *d* = 0.01, *P* = .73). 1RM of the untrained leg also increased in the groups that trained with high load (HLF: 5%, *d* = 0.27, *P* = .001; HLNF: 6%, *d* = 0.26, *P* = .009) but not in LLF (0.4%, *d* = 0.01, *P* = .74) or CON (0.2%, d = 0.01, *P* = .93) (Figure 2, see Table 1 for raw values, and Table S2 in supporting information for main effects and interactions). The increase in 1RM of the trained and untrained leg correlated *r* = .34 (*P* = .028).

3.4 | Voluntary isometric force and EMG

Before training, MVIC force and VL and RF-EMG_{RMS} were similar between groups for both legs (all *P* > .05). MVIC force increased in the trained leg in HLF (6%, *d* = 0.35, *P* = .001) and HLNF (12%, *d* = 0.67, *P* = .001) but not in LLF (−3%,

$d = 0.14$, $P = .12$) or CON (1%, d = 0.08, $P = .58$). No changes occurred in the untrained leg MVIC force (CON: 0.6%, d = 0.35, $P = .74$; LL: −0.4%, $d = 0.35$, $P = .90$; HLF: −0.3%, $d = 0.35$, $P = .85$; HLNF: 3%, $d = 0.35$, $P = .053$) (Figure 2, Table 1, and Table S2 in supporting information). The increase in MVIC force of the trained leg correlated with the increase in the trained leg 1RM ($r = .42$, $P = .006$) and the changes in untrained leg MVIC force ($r = .46$, $P = .002$).

VL-EMG$_{RMS}$ did not change in either leg. The RF-EMG$_{RMS}$ increased from baseline in the trained leg of all groups (13%, $d = 0.33$, $P = .005$) (Table 1, and Table S2 in supporting information). The changes in RF-EMG$_{RMS}$ correlated with those obtained in the trained leg MVIC force ($r = .31$, $P = .049$).

3.5 | Corticoespinal excitability

Before training, AURC-VL, AURC-RF, and AMT were similar between groups in both legs (all $P > .05$). Four weeks of RT reduced the AURC-VL in both legs in HLNF (−19%, $d = 0.44$, $P = .011$) but not in CON (17%, $d = 0.27$, $P = .13$), LLF (−14%, $d = 0.23$, $P = .12$), or HLF (−10%, $d = 0.20$, $P = .22$) (Figure 3, Table 1, and Table S2 in supporting information). No changes occurred in the AURC-RF (Figure S1 in supporting information) and AMT (Table 1, and Table S2 in supporting information). Changes in CSE in the VL or the RF were not related to changes in 1RM ($r = -.10$ and $r = -.11$, respectively, all $P > .05$) or MVIC ($r = -.03$ and $r = -.06$, respectively, all $P > .05$).

3.6 | Responses to peripheral nerve stimulation

Before training, VL or RF-M$_{max}$ and Tw-M$_{max}$ were similar between groups in both legs (all $P > .05$). M_{max} did not change in any muscle, leg, or group. Tw-M_{max} of the trained leg decreased from baseline in LL (−19%, $d = 0.74$, $P = .001$) and HLF (−10%, $d = 0.34$, $P = .022$) but not in CON (−2%, $d = 0.07$, $P = .66$) or HLNF (−0.5%, $d = 0.02$, $P = .90$). No changes occurred in the Tw-M$_{max}$ of the untrained leg (Table 1 and Table S2 in supporting information).

4 | DISCUSSION

We determined the effects of training load and fatigue on maximal voluntary force and markers of neural adaptations in the trained and untrained knee extensors. In partial agreement with the hypothesis, high- but not low-load RT improved maximal voluntary force in the trained and the untrained leg but fatigue did not further enhance these adaptations. Furthermore, voluntary force improvements were unrelated to CSE changes in both legs.

Recommendations highlight the use of training loads above a 70% of 1RM to maximize voluntary force and hypertrophy.[2] However, recently it has been shown that training loads below 60% of 1RM can also increase maximal voluntary force albeit to a lesser extent than high-load RT.[2] Our results support the greater effectiveness of high-load RT but do not support low training loads (25% of 1RM) as a training stimulus to increase maximal voluntary force in the trained leg. A recent study reported that six but not three weeks of low-load RT increased 1RM and MVIC force of the knee extensors.[26] Therefore, this suggests that when low compared with high loads are used during RT, longer training periods might be needed to produce adaptations. Thus, this slower increase in maximal voluntary force with low-load RT could explain the lack of changes after four weeks in the present study. Furthermore, the high frequency (4 days/week) used in our training protocol aiming to maximize CE could have hindered the increases in maximal voluntary force of the trained leg in the LLF group. In fact, although we allowed a long rest interval between the last training day and the POST measurements (96-120 hours), we found a decrease in the amplitude of muscle twitches obtained by electrical stimulation of the peripheral nerve. Because there were no changes in M_{max} in VL and RF, a prolonged impairment in the excitation-contraction coupling is more likely to account for the decrease in the force-generating capacity of the knee extensors than a decrease in muscle fiber membrane excitability. Indeed, previous studies reported prolonged decreases (up to eight days) in muscle twitches without changes in M_{max} after eccentric exercise.[27] Although specific eccentric exercise was not performed in the present study, the combination of training to failure, which is associated with high levels of muscle damage,[28] and the high frequency of training allowing a shorter time for recovery between training bouts, could have had a cumulative effect leading to greater levels of muscle damage affecting the force-generating capacity even after 96-120 hours of rest.

Regarding the untrained limb, this is the first study investigating the effects of training load on the CE of maximal voluntary force. Unilateral RT at 70%-100% of maximum voluntary force produced 27% (±20%) CE.[10] CE of maximal voluntary force was smaller in the present study and occurred only after RT with high loads. CE of maximal voluntary force is probably related to the training stimulus arising from the concurrent activation of the untrained hemisphere during unilateral contraction of the knee extensors.[7] The intensity of the muscle contraction is a strong modulator of the ipsilateral hemisphere activation, with strong contractions leading to greater ipsilateral hemisphere activation[11,12] and intensity-dependent reductions in intracortical inhibition and interhemispheric inhibition from the contralateral to the ipsilateral hemisphere.[11] Therefore, RT load may influence the magnitude of CE.[8] Notwithstanding, most of the previous studies used training loads above 70% of the maximum force. In addition, the few studies that used low-load unilateral RT reported inconsistent results,[20,21] limiting any conclusion about the effect of training load on CE. Our results agree with previous studies showing that very low training intensities (25% of 1RM) do not produce CE of maximal voluntary force.[21] There is a correlation between force improvements in the trained and untrained limb in previous studies,[9,17] which is also present in the current results ($r = .34$ and $r = .46$ for 1RM and MVIC force, respectively). From this correlation, it could be argued that if low-load RT produces lower increases in voluntary force of the trained limb, a lower CE of voluntary force could be expected. Therefore, the present results suggest that low-load RT is not effective in producing CE. This could be due to low activation of the ipsilateral hemisphere during unilateral low-load contractions, producing a subthreshold stimulus for CE.[29,30]

Muscle fatigue during the set could also enhance RT adaptations in the trained limb[31] by increasing metabolic stress and motor unit activation.[5] Despite our results show higher levels of perceived exertion in LLF and HLF compared with HLNF, suggesting greater levels of fatigue during the training session, 4 weeks of unilateral knee extensions at 75% of 1RM increased the trained-limb maximal force independent of muscle failure. These results agree with previous studies showing that fatigue during RT is not a necessary stimulus for increasing maximal voluntary force.[6] However, some findings suggest that training to failure could be useful for muscle hypertrophy.[6] Although we did not measure muscle hypertrophy, an increase in muscle contractile tissue would have increased involuntary muscle twitch force. However, we found a decrease in muscle twitch force induced by electrical peripheral nerve stimulation in the groups that trained to muscle failure, suggesting a reduction in muscle force capabilities. This reduction is probably a reflection of the greater levels of muscle damage derived from the combination of high levels of fatigue and training frequency,[28] as discussed above. Thus, if higher increases in muscle size occurred as a consequence of training to failure in the present study, it is likely that they were associated with greater levels of muscle damage and edema.[28,32] Therefore, although the decrease in force capabilities derived from muscle damage could have interfered with the benefits of training to failure, our results show no additional benefit on voluntary force adaptations compared with a RT protocol not reaching failure.

Notwithstanding, the novel element of the present study was the determination of the effects of muscle fatigue during the set on CE. As it was the case for training load, fatiguing submaximal unilateral contractions can also increase the level of activation of the ipsilateral hemisphere.[13] Thus, we hypothesized that RT to failure (both, with low- and high-load RT) would increase the stimulus to the untrained hemisphere, especially during the final repetitions, where the concurrent activation would be higher, therefore increasing the magnitude of CE. However, most CE studies used training protocols leading the sets to or close to muscle failure.[16-19,33] Only one study compared the effects of two training programs associated with different levels of fatigue during the training session on CE.[22] The results showed that the high- vs. low-fatigue program produced greater CE, suggesting that the level of fatigue attained during the set in the trained limb influences the

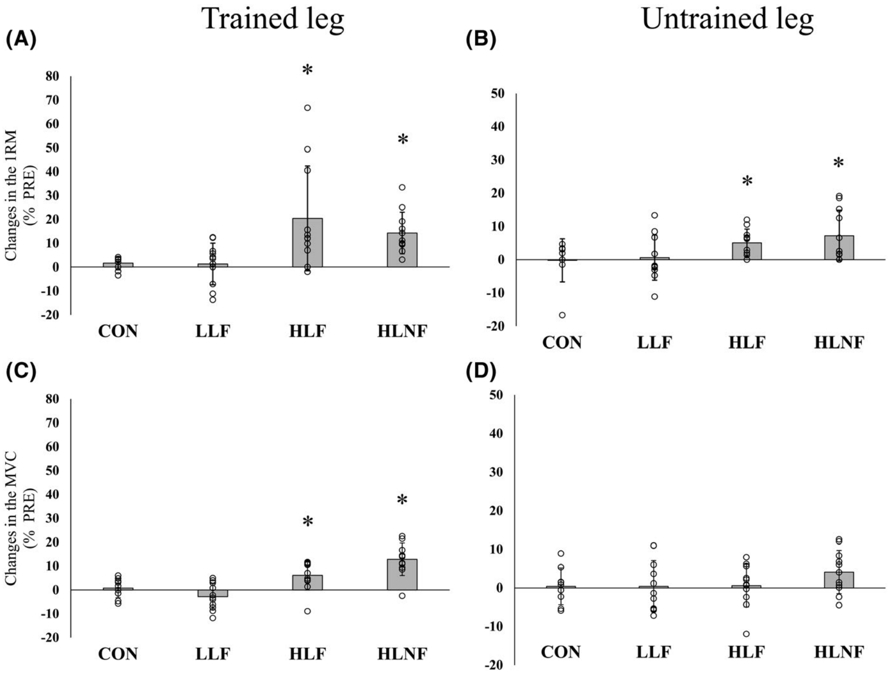

FIGURE 2 Trained (left column) and untrained (right column) mean and individual changes in 1RM (upper row) and MVIC (lower row). *A statistically significant difference ($P < .05$) to PRE values

magnitude of CE.[22] However, our results show that reaching muscle failure in each set did not produce CE with low-load RT or enhance the magnitude of CE with high-load RT. Differences in the training protocols between studies could explain the discrepant data regarding the effect of fatigue during high-load RT. The low-fatigue protocol[22] consisted of 30 repetitions performed continuously with 18.5 seconds of rest between repetitions. The rest interval between sessions allowed to maintain the same power levels during the whole training session, suggesting low levels of neuromuscular fatigue.[34] However, the high-fatigue protocol[22] (5 × 6, 10RM) was very similar to our HLNF protocol (6 sets × 5-6 reps, 75% of 1RM). Therefore, the high-fatigue protocol in our study (ie, HLF), reaching muscle failure in each set, represents the protocol leading to the greater amount of fatigue. Taken together, previous studies suggest that a minimum threshold of fatigue may be needed to maximize CE with high-load RT.[22] However, our results showing no benefit of RT to failure compared with not to failure for CE suggest that high-load RT protocols included in the present study were above the minimum fatigue threshold needed to maximize CE, and therefore, more fatigue did not translate into more CE. However, the present results agree with those from a previous complementary study with a small sample size that also found that CE of the knee extensors is not modulated by fatigue during RT.[35] Based on the contrasting findings about the sensitivity of CE to fatigue during RT in the upper[22] or lower limbs,[35] it could be the case that results may be influenced by the trained segment, being that the sensitivity is greater in the muscles of the upper limbs.[22] However, more research is needed to confirm this statement.

It is believed that neural adaptations underlie the increases in maximal voluntary force after RT.[7] Increases in CSE may lead to a better efficacy of the motor command through a greater neural drive from corticospinal neurons to the motoneurons. Meta-analytic evidence suggests that RT increase CSE in the trained limb when measured during contraction, [36] but do not change in the untrained limb.[10] However, our results do not support the role of an increased CSE as a mechanism to improve force in either leg, which agrees with previous studies that also found no changes[17,18,37] or even decreases[38] in CSE when measured at rest and during contraction in the trained limb, or no changes at rest or during contraction in the untrained limb.[10] Reductions in CSE in the trained muscles after a short-term RT have been suggested to be related to an increase in corticospinal efficiency that reduces the neural resources needed to perform the task during which measurements are obtained.[39] An increase in the force produced per motor unit may lead to a lesser activation of the overall motor unit pool to achieve the same force level; however, the twitch force in the HLNF group was unchanged (−0.5%), suggesting no changes in the force-generating capacity of the muscle. In addition, the changes in CSE occurred without significant correlations with changes in maximal dynamic or isometric voluntary force, which questions the functional link between changes in CSE and voluntary force. Furthermore, independently of the direction and magnitude of the change in CSE, only one previous study reported a correlation between changes in maximal force and increases in CSE in the untrained limb[16] and none in the trained limb. Another study reported a correlation between CSE in the untrained limb measured during contraction of the trained limb and CE.[9] An increase in the activation of the untrained hemisphere during contractions of the trained limb due to lower interhemispheric inhibition would mean a greater stimulus to the untrained hemisphere, allowing a greater CE.[9] However, the lack of correlation between changes in maximal force and CSE of the corresponding limb (either trained or untrained) agrees with previous reports of the absence of correlation between CSE and performance in ballistic contractions[40] and casts doubts about the role of CSE as a mechanism contributing to force increases. It is possible that force increases may be related to adaptations in other descending tracts with a role in force generation,[37] like the reticulospinal tract,[41,42] which could not be detected by TMS of the motor cortex, or in motor cortex structures involved in other TMS outcomes not tested in the present study (ie, changes in intracortical circuits).[17,36]

The present study has some limitations that could have influenced the results or limited the conclusions. The absolute load in the training group was maintained constant during the four weeks of training to reduce the exposure to specific 1RM test and reduce any possible confounding effect between training adaptations and test learning. Because maximal voluntary force increased after training, the initial relative training load progressively decreased, which could have reduced the training stimulus. Also, as discussed in previous paragraphs, despite POST measurements occurring after 96-120 hours of rest, the high frequency of training (4 days/week) plus training to failure led to reductions in the force-generating capacity of the muscle may be due to residual fatigue, which may have hindered any advantage of training to failure. Lastly, CSE on its own may not be an optimal measurement to index functionality of neural adaptations to RT,[36] and more information regarding neural mechanisms associated to RT could have been obtained by including other measurements like silent period or intracortical inhibition, which have been found to be reduced after short RT periods.[17,36]

Collectively, the data suggest that high- but not low-load RT improves maximal voluntary force in the trained and untrained leg and fatigue did not further enhance these adaptations. Furthermore, voluntary force improvements were

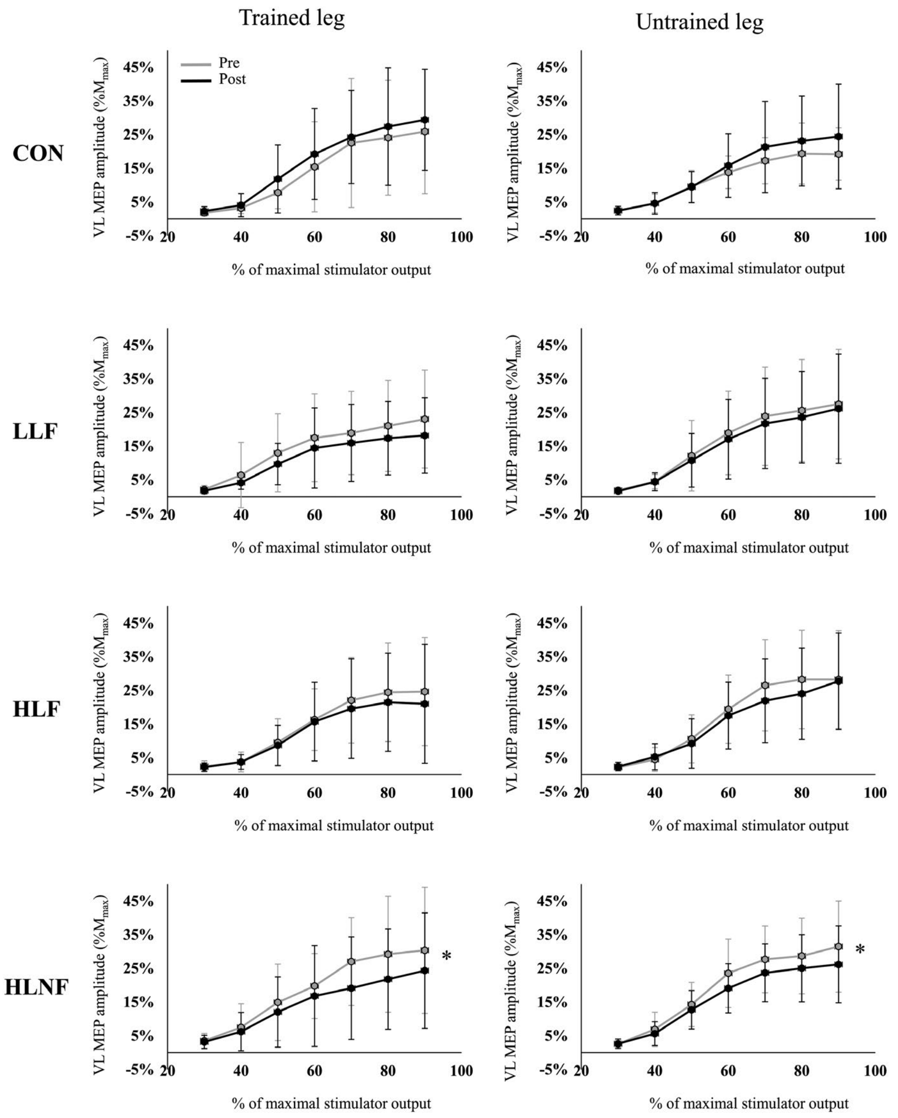

FIGURE 3 Trained (left column) and untrained (right column) leg vastus lateralis recruitment curve of each group. *A statistically significant ($P < .05$) difference between PRE to POST in the area under the recruitment curve

unrelated to CSE changes in both legs. Therefore, high levels of fatigue during high-load RT sessions aiming to improve maximal voluntary force of the untrained limb could be avoided, reducing the levels of perceived exertion and delayed day-to-day recovery while maintaining the magnitude of CE.

5 | PERSPECTIVES

People with unilateral dysfunction due to stroke or orthopedic injuries could benefit from unilateral RT as an adjuvant to standard rehabilitation programs. Therefore, it is relevant to determine which modifications in training variables are required for the adaptations in the untrained limb to occur and which modifications, if any, could maximize those adaptations. We show that short-training periods with very low loads (25% of 1RM) do not lead to CE and high loads are required to increase the force of the untrained leg extensors after 4 weeks of unilateral RT. Therefore, the means and the exercise prescription should allow an appropriate loading of the trained muscles in order to obtain the potential benefits of unilateral RT in the untrained homologous muscles. We also show that training to concentric muscular failure neither lead to CE with low loads and/or enhance CE with high loads. Therefore, training to concentric muscle failure during unilateral RT aiming to improve the maximal voluntary force of the untrained limb could be avoided in favor of less demanding programs in which sets are stopped away from failure, which could be especially relevant in those patients with already high self-reported fatigue such as stroke or multiple sclerosis.[43,44]

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CONFLICT OF INTEREST

None of the authors declare conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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