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Effects of load and fatigue during unilateral resistance training on neuromuscular adaptations.

Autor:
D. David Colomer Poveda

Directores:
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Murcia, junio de 2020

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AUTHORIZATION OF THE DIRECTORS OF THE THESIS FOR SUBMISSION

Prof. Dr. Gonzalo Márquez Sánchez, Prof. Dr. Salvador Romero Arenas and Prof. Dr. Tibor Hortobágyi as Directors of the Doctoral Thesis "Effects of load and fatigue during unilateral resistance training on neuromuscular adaptations." by D. David Colomer Poveda in the Programa de Doctorado en Ciencias del Deporte, **authorizes for submission** since it has the conditions necessary for his defense**.**

Sign to comply with the Royal Decrees 99/2011, in Murcia, 8th of June, 2020.

Gonzalo Márquez Sánchez Salvador Romero Arenas Tibor Hortobágyi

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"I would give everything I know for half of what I ignore. What little I have learned is worthless, compared to what I ignore and do not despair in learning"

René Descartes

This thesis is a compendium of three articles already published in peer-reviewed journals plus one article under review. The references for the articles are:

Article 1

Colomer-Poveda D, Romero-Arenas S, Lundbye-Jensen J, Hortobagyi T, Marquez G. Contraction intensity-dependent variations in the responses to brain and corticospinal tract stimulation after a single session of resistance training in men. Journal of applied physiology (Bethesda, Md : 1985). 2019;127(4):1128-39. doi: 10.1152/japplphysiol.01106.2018

Article 2

Colomer-Poveda D, Romero-Arenas S, Keller M, Hortobagyi T, Marquez G. Effects of acute and chronic unilateral resistance training variables on ipsilateral motor cortical excitability and cross-education: A systematic review. Physical therapy in sport: official journal of the Association of Chartered Physiotherapists in Sports Medicine. 2019;40:143-52. doi: 10.1016/j.ptsp.2019.09.006.

Article 3

Colomer-Poveda D, Hortobagyi T, Keller M, Romero-Arenas S, Marquez G. Training intensity-dependent increases in corticospinal but not intracortical excitability after acute strength training. Scandinavian journal of medicine & science in sports. 2020;30(4):652-61. doi: 10.1111/sms.13608

Article 4

Colomer-Poveda, D., Romero-Arenas, S., Fariñas, J., Iglesias-Soler, E., Hortobágyi, T., Márquez, G. Training load but not fatigue affects cross-education of maximal voluntary force (under review).

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ABBREVIATIONS

The abbreviations of the units from the International System Units and the abbreviations universally used in statistics are not included in this section, as there are internationally accepted standards for their use.

AMT	Active motor threshold.
AURC	Area under the recruitment curve.
BB	Biceps brachii.
CE	Cross education
CMEP	Cervicomedullary motor evoked potential
CON	Control group or control condition.
CS	Conditioning stimulus
CSE	Corticospinal excitability
D-wave	Direct wave.
EMG	Surface electromyography
EMG$_{RMS}$	Electromyography root mean square
ERT	Estimated resting twitch
FDI	First dorsal interosseous
GABA	Gamma aminobutyric acid
HLNF	High load resistance training without failure group.
HLF	High load resistance training to failure group.
H-reflex	Hoffmann's reflex
ICF	Intracortical facilitation
IHI	Interhemispheric inhibition
ISI	Inter stimulus interval
I-wave	Indirect wave.
LL	Low load resistance training group.
LMEP	Lumbar motor evoked potential.

LTP	Long-term potentiation.
M1	Primary motor cortex.
MEP	Motor evoked potential
M_{max}	Maximal compound muscle action potential
MVC	Maximal voluntary contraction.
M-wave	Compound muscle action potential elicited by electric stimulation of the peripheral nerve.
RC	Recruitment curve.
RF	Rectus femoris.
1RM	One repetition maximum.
10RM	Ten repetition maximum.
RM-ANOVA	Repeated measures analysis of variance.
RMT	Resting motor threshold.
RPE	Ratings of perceived exertion
RT	Resistance training.
SICI	Short-interval intracortical inhibition
SP	Silent period.
ST	Strength training.
TES	Transcranial electric stimulation
TMEP	Thoracic motor evoked potential.
TMS	Transcranial magnetic stimulation.
TS	Test stimulus.
VL	Vastus lateralis.
V-wave	Volitional wave.

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ABSTRACT

When resistance training (RT) is performed unilaterally, increases in maximal voluntary force occur in the trained and also in the untrained homologous contralateral muscle, a phenomenon known as cross-education of voluntary muscle force. It is believed that cross-education arises from neural adaptations in the untrained hemisphere consequence of its concurrent activation along with the trained hemisphere during unilateral contractions. The magnitude of cross-education is estimated to be around a 12% of the maximal voluntary force, which could be considered of small clinical relevance. RT variables like training load and fatigue during the set influence the concurrent activation of the untrained hemisphere during unilateral contractions, and may be manipulated to increase the magnitude of cross-education. Therefore, the main aim of this thesis was to determine the effect of RT load and the level of fatigue during the set, on cross-education and the acute neural changes in cortical and corticospinal circuits projecting to the trained and untrained muscles. Those acute changes occurring after just one RT session are believed to be the trigger for the long-term sustained neural adaptations leading to voluntary force increases. In the first study, we determined the effects of RT load on the acute trained biceps brachii responses to transcranial magnetic and cervicomedullary electric stimulation after a RT session. We found an increase in the responses to both types of stimulations after RT. However, training load only affected the responses to transcranial magnetic stimulation, with greater increases in the responses after high-load RT. This data suggests that RT load influence the acute increases in cortical excitability. In the second study, we performed a systematic review to analyse the unilateral RT variables that may affect the neural adaptations in the untrained hemisphere. We found that unilateral RT increases cortical excitability and reduces intracortical inhibition. However, results were inconsistent probably due to the influence of training variables like contraction type, training load, fatigue or the strategy of pacing the movement, which influence the adaptations in the untrained hemisphere. In the third study, we determined the effect of acute RT load on the

trained and untrained biceps brachii corticospinal excitability and the efficacy of intracortical circuits after a single RT session. We found that acute high- but not low-load unilateral RT increases corticospinal excitability in the trained muscle without modifications in intracortical inhibition or facilitation. However, the effects of a single session of RT were limb-specific, as no changes occurred in the untrained hemisphere regardless of training load. In the fourth study, we determined the effects of training load and the level of fatigue during the set on cross-education and associated chronic neural adaptations after four weeks of RT. We found that high- but not low-load RT improves maximal voluntary force in the trained and the untrained knee extensors but fatigue did not enhance these adaptations. Furthermore, voluntary force improvements were unrelated to corticospinal excitability changes in both legs. Overall, this thesis shows that training load influences the chronic functional adaptations in the trained and the untrained side after RT. However, despite the influence of training load on the acute changes in CSE, suggesting a greater influence of high-load RT on supraspinal structures, chronic voluntary force improvements after short-term RT are not related to changes in CSE. The corticospinal excitability of the untrained hemisphere does not change either after one session or four weeks of RT regardless of training load, probably due to the lower stimulus that the untrained hemisphere receives. Furthermore, fatigue during RT, which may increase the concurrent activation of the untrained hemisphere, does not have an additive effect on the adaptations in the untrained side and therefore could be avoided.

Keywords: Cross-education, Unilateral Resistance Training, Transcranial Magnetic Stimulation, Corticospinal excitability, Cortical excitability.

RESUMEN

El entrenamiento de fuerza (EF) unilateral aumenta la fuerza voluntaria máxima tanto del músculo entrenado, como del músculo homologo contralateral no entrenado, un fenómeno conocido como efecto cruzado. El efecto cruzado surge de adaptaciones neurales en el hemisferio no entrenado como consecuencia de su activación concurrente junto con el hemisferio entrenado durante contracciones unilaterales. La magnitud del efecto cruzado se estima en un 12% de la fuerza voluntaria máxima, lo que se podría considerar de baja relevancia clínica. Variables relacionadas con el EF como la intensidad y la fatiga durante la serie influyen sobre la activación concurrente del hemisferio no entrenado durante contracciones unilaterales, por lo que podrían ser manipuladas para aumentar la magnitud del efecto cruzado. Por tanto, el principal objetivo de esta tesis es determinar el efecto de la intensidad de entrenamiento y el nivel de fatiga durante la serie sobre el efecto cruzado y los cambios neurales agudos en los circuitos corticales y corticoespinales que proyectan sobre el miembro entrenado y no entrenado. Se piensa que estos cambios agudos, que ocurren tras una única sesión de EF, podrían ser los detonantes de las adaptaciones neurales sostenidas a largo plazo que dan lugar a los aumentos en la fuerza voluntaria. En el primer estudio, determinamos los efectos de la intensidad del EF en las respuestas agudas del bíceps braquial a la estimulación magnética transcraneal y eléctrica cervicomedular tras una sesión de EF. Encontramos un aumento en la respuesta a ambos tipos de estimulación. Sin embargo, la intensidad de entrenamiento solo afectó a la respuesta a la estimulación magnética transcraneal, observándose mayores aumentos en las respuestas tras EF de alta intensidad. Estos datos sugieren que la intensidad del EF afecta a la excitabilidad cortical. En el segundo estudio, realizamos una revisión sistemática para analizar qué variables del EF podrían afectar a las adaptaciones neurales del hemisferio no entrenado. Encontramos que el EF unilateral aumenta la excitabilidad cortical y disminuye la inhibición intracortical. Sin embargo, se observó una falta de consistencia en los resultados, probablemente debido a la influencia de variables de entrenamiento

como el tipo de contracción, la intensidad de entrenamiento, la fatiga o la estrategia para el control del tempo durante el movimiento, las cuales influyen sobre las adaptaciones del hemisferio no entrenado. En el tercer estudio, determinamos el efecto de la intensidad de entrenamiento en la excitabilidad corticoespinal y la eficacia de los circuitos intracorticales del bíceps braquial entrenado y no entrenado tras una sesión de EF. Encontramos un aumento en la excitabilidad corticoespinal del músculo entrenado tras EF de alta intensidad pero no de baja intensidad, sin cambios en la inhibición o facilitación intracortical. Sin embargo, los efectos de una sola sesión de EF fueron específicos del miembro entrenado, pues no se halló ningún cambio en el hemisferio no entrenado independientemente de la intensidad de entrenamiento. En el cuarto estudio, determinamos el efecto de la intensidad de entrenamiento y el grado de fatiga durante la serie en el efecto cruzado y las adaptaciones neurales crónicas derivadas de un periodo de cuatro semanas de EF. Observamos que el entrenamiento de fuerza de alta intensidad, no así el de baja intensidad, mejoró la fuerza voluntaria en los extensores de rodilla entrenados y no entrenados, sin que la fatiga durante la serie influyera en dichas adaptaciones. Además, los aumentos en la fuerza se relacionaron con cambios en la excitabilidad corticoespinal de ambas piernas. Esta tesis muestra que la intensidad de entrenamiento influye en las adaptaciones funcionales derivadas del EF. Sin embargo, a pesar de la influencia de la intensidad de entrenamiento en los cambios agudos en la excitabilidad corticoespinal, la cual sugiere una mayor influencia del EF de alta intensidad sobre estructuras supraespinales, los aumentos crónicos en la fuerza tras un periodo corto de EF no se asocian con cambios en la excitabilidad corticoespinal. La excitabilidad corticoespinal del hemisferio no entrenado no cambió ni tras una sesión ni tras cuatro semanas de EF independientemente de la intensidad de entrenamiento, probablemente debido al menor estímulo que recibe. Además, la fatiga durante el EF, la cual puede aumentar la activación concurrente del hemisferio no entrenado, no tiene ningún efecto aditivo en las adaptaciones del miembro no entrenado y por tanto puede evitarse.

Palabras clave: Efecto cruzado, Entrenamiento de Fuerza Unilateral, Estimulación magnética transcraneal, Excitabilidad corticoespinal, Excitabilidad cortical.

I – GENERAL INTRODUCTION

I - GENERAL INTRODUCTION

Resistance training (RT) is one form of motor training widely used to increase sports performance (1-4), improve health (5-14), and to diversity recreational training programs. RT increases maximal voluntary force and muscle mass (15, 16). When RT is performed unilaterally (i.e. with only one limb while the contralateral homologous is at rest), increases in maximal voluntary force occur in the trained and also in the untrained homologous contralateral muscle, a phenomenon known as cross-education (CE) of voluntary muscle force (17-20).

Maximal voluntary force can increase already after short periods of unilateral RT without any apparent hypertrophy in either limb (21-25). The dissociation between the time course of increase in muscle mass and maximal voluntary force has been interpreted as an indirect evidence that early increases in maximal voluntary force in the trained and untrained muscles are consequence of adaptations in the nervous system (26-28). Non-invasive stimulation techniques like transcranial magnetic stimulation (TMS) (29-46), or direct stimulation of the corticospinal axons (34, 47, 48) and a peripheral nerve (49-59), allowed researchers to track specific neural adaptations to RT at different levels of the nervous system (60). Although the main locus of neural adaptations underlying maximal voluntary force increases in the trained muscles is still a matter of debate and may involve adaptations at the spinal and supraspinal level (61, 62), the neural adaptations leading to CE are believed to be located at the untrained hemisphere (63-69). Those adaptations may arise from the lower but concurrent activation of the ipsilateral (to the contracting muscle) untrained hemisphere along with the trained hemisphere (70-73). For example, several TMS studies reported that short term RT is accompanied by increases in corticospinal excitability (CSE) or reductions in intracortical inhibition in the trained and the untrained hemisphere (33, 38-41, 74). Those neural adaptations theoretically would increase the effectiveness of the motor command and the central drive to the muscles, leading to early increases in maximal voluntary force. In fact, such adaptations can occur as fast as after just one RT session (75-78), before any maximal voluntary force

improvement could be measured. Those acute neural changes after a bout of RT have been interpreted as the initial neural adaptations to RT that may trigger the sustained neural adaptations underlying the increases in maximal voluntary force in the trained and the untrained muscles (i.e. CE) if the stimulus is repeated in time (75-77).

Independently of the underlying mechanisms, from a practical point of view, CE could be used as an adjuvant to standard rehabilitation programs to accelerate recovery in people with unilateral dysfunctions consequence of orthopaedic injuries or strokes (79-81). However, the magnitude of CE is estimated to be around 12%, which could be considered of small clinical relevance (18). Furthermore, unilateral orthopaedic injuries or strokes are associated with brain remodelling that reduce the excitability of the hemisphere controlling the affected limb (82-87), which could reduce even more the effect of CE on those populations. Therefore, there is a need to maximize the benefits that the untrained limb gets from the unilateral training of the homologous contralateral muscles.

CE of voluntary force could be enhanced by increasing sensory inputs to the untrained hemisphere by viewing the reflection of the trained limb in a mirror (88, 89), with whole body muscle vibration (90) or by somatosensory stimulation (91). CE could also be optimized by increasing the concurrent activation of the untrained hemisphere during unilateral contractions by priming the primary motor cortex (M1) with non-invasive brain stimulation techniques, such as anodal transcranial direct current stimulation (92-94). However, before exploring new tools added to unilateral RT to enhance CE, may be worth it to examining the effects of the modification of some basic training variables on CE, to determine the training protocol most efficacious in increasing maximal voluntary force of the untrained limb.

Adaptations to RT in the trained side are determined by RT variables such as load (95-97), volume (98-100), frequency (101, 102) and the degree of fatigue during the set (103-107). However less is known about the ideal exercise prescription to optimize CE of voluntary muscle force. Variables like the type of muscle contraction (108, 109), the total volume performed during training, or the velocity of such contractions during dynamic RT has been shown to affect the magnitude of CE (110). Specifically, eccentric contractions, greater training volumes, and high contraction speeds seems to enhance of CE (108-110). Because

CE is thought to be related to neural adaptations in the untrained hemisphere consequence of its concurrent activation during unilateral contractions (66-68), it is likely that modifications in training variables that lead to a greater concurrent activation of the untrained hemisphere may enhance the functional and neural adaptations in the untrained limb (111). This may explain, for example, why eccentric contractions, which are associated with a greater concurrent activation of the untrained hemisphere than isometric or concentric contractions (112, 113), lead to a greater CE of voluntary muscle force (108, 109). However, there is a lack of knowledge about how modifications in other relevant training variables could affect adaptations in the untrained limb (111). Variables like RT load or the level of fatigue during the set may affect the adaptations in the untrained hemisphere underlying CE (111). In fact, high contraction intensities (70, 114, 115), and high levels of fatigue (71), separately, lead to a greater concurrent activation of the untrained hemisphere , which could potentially increase the magnitude of CE. If the last statement is true, greater training loads and levels of fatigue during RT could be suitable as CE-enhancer for orthopaedic patients. However, greater levels of fatigue would have limited relevance for neurological patients (stroke, multiple sclerosis), who have high levels of self-reported fatigue (116, 117), and therefore other ways of enhancing CE should be used.

Therefore, **the main aim of this thesis was to determine the effect of training load and the level of fatigue during RT on the CE of voluntary force that occurs with unilateral RT in healthy adults.** We have selected both, training load and fatigue, based on their potential to influence the level of concurrent activation of the untrained hemisphere, and because we detected, in the systematic review of the present thesis (111), a lack of knowledge regarding the effect of modification of those variables on functional and neural adaptations of the untrained limb. Furthermore, early maximal force improvements in the trained and the untrained muscles are believed to be a consequence of neural adaptations (15, 27, 60, 62), which seems to occur as soon as after only one RT session (75, 77, 118). Therefore, knowing how modification in RT variables affects acute (after one session) corticospinal changes could help to infer the long-term effectiveness of RT protocols with different characteristics. Thus, the **second aim is to determine the effects of unilateral RT load on acute changes in cortical and corticospinal circuits projecting to the trained and the untrained muscles**. A

detailed understanding of the effects of training load and the degree of fatigue during the set on functional and neural adaptations will guide RT prescription aiming to optimize adaptations in the untrained limb, which could ultimately increase the potential use of CE as an adjuvant therapy in patients unable to train bilaterally.

In addition, in the general literature review of the present thesis, there is an overview of the modulation of the nervous system output during muscle contractions, after an acute bout of RT, and after chronic periods of RT in the trained and the untrained muscle, and how this output is affected by the contraction intensity or training load, and fatigue. Additionally, this initial literature review briefly introduces the main non-invasive stimulation techniques and associated measures used to monitor the neural control of voluntary muscle force and neural adaptations to RT.

II – LITERATURE REVIEW

II – LITERATURE REVIEW

2.1 TECHNIQUES TO MONITOR CHANGES IN THE NERVOUS SYSTEM OUTPUT

2.1.1 Transcranial magnetic stimulation

First registered successful attempts to stimulate the human cortex date from 1874, when Bartholow observed limb muscle contractions in a woman undergoing electric stimulation with fine needles inserted in her brain through an ulcer in the skull (119). This stimulation technique allowed a detailed mapping of the cerebral cortex, leading to the localization of the motor areas (120, 121). However, this invasive technique was limited to patients undergoing a brain surgery. It was not until 1980, when Merton developed a transcranial electric stimulation (TES) technique that allowed a successful stimulation of the cerebral cortex of subjects with intact skull (122, 123). Although TES was a step forward because of its non-invasive nature, it uses brief high voltage shocks delivered through electrodes attached to the scalp that produce a strong uncomfortable sensation. Five years later, Barker and co-workers developed another non-invasive, safe, and painless technique to stimulate the intact human brain, TMS (124). Since its invention, this method has been widely used in the field of neuroscience to study general and pathological brain physiology and motor control.

A transcranial magnetic stimulator is a capacitor charged by a power supply that can be discharged through a coil of wire creating a current of around 4000 A (124, 125). According to the principle of electromagnetic induction, the high-intensity current flowing through the coil generates a magnetic field of about 2-4 Tesla lasting 100μs passing perpendicularly to the plane of the coil (126, 127). When the coil connected to the stimulator is placed over the scalp, the magnetic field passes through the skull and generates a secondary electric current perpendicular to the magnetic field that depolarizes the neurons of the brain under the coil (127). The shape of the coil influences the depth and focus of the magnetic field and therefore of the stimulation (128, 129). The three most common

types of coils used are the circular coil, the figure of eight coil (or Butterfly coil), and the double cone coil (130). The circular coil has usually an 8-10 cm diameter and generates a powerful magnetic field that is stronger near to the circumference and weaker near the center of the coil, which means that stimulation occurs on a wide surface under the coil (128). The "figure of eight" coil consists of two circular coils placed side by side. With this type of coil the strength of the magnetic field is greater at the intersection of the two coils, which allows a more focal stimulation than the circular coils (128). The double cone coil is like a figure of eight coil but with the two coils side by side with an angle, which increases the strength of the magnetic field at the intersection, allowing a deeper stimulation (131). These coils are usually used to stimulate tissue on the central sulcus, where the cortical representations of the lower limb muscles are located (131).

Although both types of transcranial stimulation, electric and magnetic, seem to differ only in the way that they produce the ion flow in the tissue underneath, they also differ in the site at which each stimulation activates the corticospinal system (132-134). Studies recording the descending corticospinal volley evoked by TES and TMS with epidural electrodes in the spinal cord, have shown that the descending volley is formed by a series of waves whose characteristics are affected by the type and intensity of stimulation (133). With TES the response is composed mainly by an initial direct wave (D-wave), and only with greater intensities of stimulation, a second indirect wave (I-wave) with a greater latency (1.5 ms later) appears (134). However, with TMS, the response follows an inverse pattern. With low stimulation intensities, the response is mainly composed by an early I-wave, followed by later I-waves when the stimulation intensity is increased. The preceding D-wave only appears with high intensities of TMS (134). It is thought that D-waves arises from the deeper direct activation of the descending axons of the corticospinal neurons, whereas the I-waves are the consequence of the activation of the corticospinal neurons trans-synaptically by cortical interneurons activated by the TMS (134). The differences between the site of stimulation of TES and TMS explain the longer latency of the TMS response at low and medium intensities of stimulation (135).

According to the somatotopic organization of the M1 (120, 121), the response to TES or TMS also depends on the position of the electrodes or the coil over the scalp. With TMS, the coil could be easily moved through the scalp to find

the region where the response of a given muscle is greater, which is usually called "hot-spot". Therefore, although not purely focal, TMS could be used to stimulate muscles over specific regions of the body such as the hand, forearm, upper arm, legs, face, etc. With high enough intensity, single pulse TMS produces twitches in contralateral muscles and, when used with surface electromyography (EMG), a motor evoked potential (MEP) is registered in the muscle under study and nearby muscles due to the overlap of cortical representations in the M1 (126, 130). The MEP is as EMG signal composed by the action potentials of the motor units stimulated by the descending volley coming from the corticospinal neurons activated by the cortical neurons depolarized by the single pulse TMS (126, 130).

Because of the cortical origin of the MEP obtained by TMS, the size of the MEP has been interpreted as a measure of cortical excitability (130). However, although one of the factors that modulates the size of the MEP is the excitability of the cortical neurons activated initially by the single pulse, there are other factors in the pathway from the brain to the muscle that could also influence the MEP size (60, 136, 137). Those factors include mainly the excitability of the spinal α-motoneurons, and peripheral factors affecting the features of the recorded muscle fibres action potentials forming the MEP, such as the electrode position or the muscle fibre membrane properties (136, 138). To reduce the influence of the peripheral factors, the MEP amplitude is usually normalized with the amplitude of the maximal compound muscle action potential (M_{max}) obtained by electric stimulation of the peripheral nerve innervating the muscle under study (138). However, even normalized MEPs are still influenced by spinal factors, therefore they should be considered as a measure of corticospinal rather than pure cortical excitability (60, 136). To further delimit the origin of the modulation of the MEPs at the cortical or spinal level, a valid measure of α-motoneuron excitability should be obtained, like MEPs obtained by electric stimulation of the corticospinal axons at the cervicomedullary junction, which will be further explained in the next section.

In addition to cortical, spinal and peripheral factors, the other main variable influencing the MEP size is the stimulation intensity (126). The intensity of the stimulus depends on the magnitude of the magnetic field generated under the coil, which can be manipulated by modifying the intensity of the current that flows through the coil (126). This intensity can be expressed in absolute values as

the percentage of the maximal stimulator output or, more often, as a percentage of the minimum output of the stimulator needed to obtain a clear response in the muscle under study (139). This minimum intensity is known as resting motor threshold (RMT), when the subject is tested at rest, or active motor threshold (AMT), when measures are obtained during a sustained low intensity muscle contraction (126, 139). The motor threshold is usually defined as the minimum intensity that produces a MEP of a peak-to-peak amplitude of 50-100 μV (RMT) or 100-200 μV (AMT) in five of ten consecutive stimulations (139).

When single pulse TMS stimulation is performed during a sustained muscle contraction, following the MEP there is a total or partial reduction in the EMG activity in the muscle that is called "silent period" (SP) (140). The SP is usually quantified as the duration of the suppression of the EMG, from the stimulus artefact, or the onset or the offset of the MEP, to the return of the voluntary activity (141). Although SP is usually used as a measure of intracortical inhibition, it is affected by both spinal and cortical inhibitory mechanisms (142). Specifically, the first part is thought to be a consequence of reduced α-motoneuron excitability; while the late part is mainly caused by the action of inhibitory gamma aminobutyric acid (GABA)-B intracortical circuits (142).

In addition to single pulse measurements, TMS allows to deliver a pair of pulses with the same or different coils located at the scalp, which is called paired pulse TMS. The first pulse is usually called "conditioning stimulus" (CS), and the second pulse "test stimulus" (TS), and are separated by a brief inter stimulus interval (ISI) (126). The effect of the CS on the TS depends on the ISI and the intensity of stimulation of the CS and the TS (126, 143, 144). Paired pulse TMS is usually used to test the efficacy of inhibitory or facilitatory intracortical circuits. The net effect of the cortical inhibitory or facilitatory circuits activated by the subthreshold CS on the TS is quantified by comparing the size of the MEP evoked by the TS alone with the MEP evoked by the TS preceded by the CS (126). When the CS precedes the TS by an ISI of 1-5 ms and the intensity of the CS is around a 70-90% of the motor threshold, there is a reduction in the amplitude of the MEP evoked by a suprathreshold TS (145). This paradigm is called short-interval intracortical inhibition (SICI). It is though that SICI arise from the activation of low-threshold cortical inhibitory GABA-A circuits by the CS, that reduce the indirect activation of the corticospinal neurons by the cortical neurons

depolarized by the TS, thus reducing the size of the MEP evoked by the TS (146). When the subthreshold CS and the suprathreshold TS are separated by an ISI of around 8-30 ms, there is an increase in the amplitude of the MEP evoked by the TS (144, 145). This paradigm, known as intracortical facilitation (ICF), is thought to arise from the recruitment of glutamatergic circuits in the M1 (144, 147). Paired pulse stimulation can also be used with two different coils to stimulate different parts of the brain (144). One possibility is to put the coils at the cortical representation of contralateral homologous muscles located in the left and right hemispheres to test interhemispheric inhibition (IHI) (148). With this paradigm, the CS and the TS are separated by an ISI of 6-50 ms, and are both suprathreshold (around 120% of the motor threshold) (148). IHI is used to test the efficacy of the excitatory transcallosal inputs from the hemisphere stimulated by the CS that projects to inhibitory GABAergic intracortical circuits located at the hemisphere receiving the TS, reducing the size of the MEP (149, 150).

2.1.2 Direct subcortical stimulation of corticospinal axons

Every voluntary, reflex or artificially stimulated motor signal will converge at the α-motoneuron pool, which was defined by Sherrington as the final common path of the nervous system (151). Therefore, when stimulation techniques are used to monitor changes in the nervous system output, α-motoneuron excitability will influence the response to stimulation, even when the stimulation occurs at the cortical level, as occurs with TMS. Thus, knowing the excitability state of the α-motoneurons helps to determine if the modulation of the nervous system output that may occur under some situations or after some interventions, has its origin at the spinal level. α-Motoneuron excitability is determined by several factors, such as the ionotropic drive (excitatory or inhibitory) coming from supraspinal centers or sensory receptors, and the properties of the α-motoneurons, which are not fixed and can be modified by neuromodulatory inputs coming from the brain stem (152). However, independently of the mechanisms determining α-motoneurons excitability, the likelihood and magnitude of α-motoneurons response to an input can be

measured by direct subcortical stimulation of the corticospinal axons (48, 153, 154).

The descending axons of the corticospinal neurons can be non-invasively stimulated at the cervicomedullary junction (154, 155), when the focus are the muscles of the upper limbs, and at the thoracic (156) or lumbar spine to focus on muscles of the legs (157). The stimulation of the corticospinal neurons at the subcortical level is accompanied by a MEP and a twitch that reflects the sum of the forces of several muscles acting around the same joint due to the non-focal nature of this stimulation technique (48, 153). The MEP is usually known as cervicomedullary MEP (CMEP) (155), thoracic MEP (TMEP) (156) or lumbar MEP (LMEP) (157) depending on the site of stimulation. The latency of the MEP obtained by subcortical stimulation of the corticospinal axons is lower than the MEP obtained by TMS, because stimulation occurs at a lower level of the corticospinal tract (155). However, despite the different site of stimulation, when a single pulse TMS is paired with subcortical stimulation of the corticospinal axons at an appropriate interval, the size of the MEP obtained by TMS is largely reduced by the antidromic collision generated by the subcortical stimulation, suggesting that both techniques recruit the same corticospinal axons (154-157). In addition, the response to subcortical stimulation of the corticospinal axons is mainly monosynaptic (158), and is not affected by afferent presynaptic inhibition or cortical excitability, as occurs with the Hoffmann's reflex (H-reflex) or the response to high intensity TES, respectively (153). This makes subcortical stimulation of the corticospinal axons the ideal technique to test α-motoneuron excitability (153).

Subcortical stimulation of the corticospinal axons could be achieved with electric and magnetic stimulation interchangeably, with the only difference that magnetic stimulation is less painful but responses are usually smaller (48, 153). To stimulate the corticospinal axons subcortically with electrical stimulation, a pair of electrodes should be placed at the mastoid processes, while with magnetic stimulation, a double cone coil should be placed over the inion (48, 153). Independently of the kind of stimulation used, the main problem with subcortical stimulation of the corticospinal axons, in addition to pain, is the risk of directly stimulating the α-motoneurons postsynaptically (137). When this happens, there is a sudden reduction of around 1-2 ms in the latency of the MEP and a lower

increase in the size of the MEP when obtained during voluntary contractions. This reflects that α-motoneurons are being directly stimulated at their axons and not transynaptically. Thus, the resultant MEP is less sensitive to changes in α-motoneuron excitability. Because the direct activation of the α-motoneuron axons by the electric stimuli occurs closer to the cathode, with cervicomedullary electric stimulation it is generally recommended to put the anode on the side of the muscles being tested to reduce the risk of direct α-motoneuron axons stimulation (48).

2.1.3 Electric stimulation of a peripheral nerve

When using any kind of stimulation to test the nervous system output in a given situation, it could be tempting to ascribe changes in the MEPs only to modulations at a spinal or supraspinal level (60). However, responses to stimulation are usually registered from the muscles using EMG. Therefore, modulations in the EMG responses to all forms of stimulation are also affected by changes in the peripheral factors that affect any form of EMG signal independently of the voluntary, reflex, or stimulated origin (138, 159). The main peripheral factors that influence EMG based signals are decreases in muscle fibre conduction velocity, or the modification of the sarcolemma excitability due to decreases in the sodium-potassium pump efficiency of the muscle membrane (138). In addition, when the amplitude of EMG signals obtained by stimulation is going to be compared between different days, factors like electrode position over the muscle, or modifications in the composition of the tissue under the EMG electrodes could also affect the signal (138). Therefore, the MEPs size obtained by TMS or cervicomedullary electric stimulation, for example, could change despite any modulation occurring at the spinal or cortical level, solely due to peripheral factors.

One way to reduce the influence of any peripheral factor on MEPs size is to normalize them with the maximal compound muscle action potential, also called the M-wave (138). The M-wave is the sum of the dispersed action potentials of the motor units located under the EMG electrodes that have been activated by a single pulse electrical stimulation of their α-motoneuron axons at a peripheral nerve (138). The M-wave informs about the peripheral properties of the

neuromuscular system without influence from spinal or cortical factors, what allows to differentiate if the cause of the modulation in a EMG derived signal, like the MEPs obtained by TMS, is due to peripheral or central factors (138). To obtain an M-wave is usual to determine its maximal amplitude (i.e. M_{max}) by increasing the electric stimulation intensity until no further growth is observed despite additional increases in stimulation intensity (138). When the minimum intensity to obtain the M_{max} is determined, it is usual to use a supramaximal stimulation intensity to ensure the depolarization of all α-motoneuron axons (138).

In addition to purely peripheral factors, electrical stimulation of the peripheral nerves can also inform about spinal factors influencing the nervous system output (160, 161). When a mixed nerve (containing afferents and α-motoneuron axons) is stimulated at intensities below the ones producing a direct stimulation of the α-motoneurons axons, the axons of the greater diameter IA afferents are depolarized (160, 161). The activation of those afferents produces a synaptic activation of the α-motoneurons at the spinal cord, causing a muscle twitch and an evoked potential, called H-reflex, which can be registered by EMG (160, 161). The H-reflex, first described by Hoffman (162, 163), has been misinterpreted as a measure of pure α-motoneuron excitability, however, the amplitude of the H-reflex is also affected by factors such as presynaptic inhibition of the IA afferents projecting to α-motoneurons (164). The amplitude of the H-reflex increases with the intensity of stimulation. However, when the intensity of stimulation is high enough to directly depolarize the α-motoneurons axons, there is a progressive decrease in the H-reflex amplitude until it disappears with higher intensities (50, 160). The cancellation of the H-reflex occurs because the direct activation of α-motoneurons provokes antidromic (from the point of stimulation to the spinal cord) impulses in their axons that collide with the orthodromic volley generated by the synaptic activation of the α-motoneurons by the IA afferents (i.e. the H-reflex) (50, 160). However, Upton et al. (165), discovered that with supramaximal stimulations leading to a M_{max} and a total cancelation of the H-reflex, the latter can also be recorded during voluntary contractions, what is called the volitional wave (V-wave). The V-wave can be registered because the orthodromic volitional volley leading to the voluntary contraction collides with the antidromic volley generated by the supramaximal stimulation of the α-motoneuron axons (137, 165). This collision allows the impulses generated by the

stimulation of the α-motoneurons by the IA afferents to reach the muscle, leading to the V-wave. The amplitude of the V-wave, which is a variation of the H-reflex obtained during contraction, is also affected by α-motoneuron excitability and presynaptic inhibition of the IA afferents (137). The size of the V-wave is affected by the intensity of the contraction, which determines the descending volley that will clear the α-motoneuron axons ultimately allowing the V-wave to be registered (137). Therefore during maximal contractions the V-wave has been proposed to reflect the magnitude of the volitional drive from supraspinal centers (49). A further description of the details of the H-reflex or the V-wave is outside the scope of the present literature review due to those techniques are not used in the experimental studies of the present thesis. For further details see (160, 161).

2.2 CORTICOSPINAL MODULATION DURING VOLUNTARY CONTRACTIONS

The present section briefly describes how the output of the nervous system to a contracting muscle is modulated depending on the characteristics of the contraction by interpreting the information obtained with the techniques described in the previous section. There are several characteristics of voluntary movements that affect the neural output, such as the frequency and the velocity during repetitive movements, the complexity of the task, the limb position, the type of contraction (113, 166-172), etc. However, in this section we focused on the two variables that are the focus of the present thesis, the intensity of the muscle contraction and fatigue during sustained or repeated muscle contractions.

2.2.1 Corticospinal modulation during contractions of different levels of voluntary muscle force

The force generated against a load or an immovable resistance (i.e. contraction intensity) is determined by the summed force exerted by every muscle acting around one or several joints (in addition to the contribution of passive tissue elements). The force exerted by these muscles will depend on the number of recruited motor units, which follow the size principle, and the firing rate (number of pulses per second) at which each motor unit fires (i.e. α-motoneuron output) (173, 174). This α-motoneuron output will depend on the

summed excitatory and inhibitory supraspinal and afferent inputs, and on α-motoneurons intrinsic properties, which can be modulated by neuromodulatory inputs (152). However, one of the main determinants of force during simple voluntary movements, is the monosynaptic corticospinal input coming from motor areas through the descending pyramidal neurons (175). The stimulation techniques described in the previous section allow to obtain information about how the corticospinal output, and the α-motoneuron excitability, are modulated during simple voluntary movements of different forces.

When responses to TMS are obtained during voluntary contractions there is an increase in the amplitude and a reduction in the latency compared to responses to an equal input obtained at rest (176-178). During voluntary contractions of different forces, the general pattern of modulation of the MEPs obtained by TMS is an initial increase in the amplitude together with contraction intensity, followed by a stabilization despite further increases in force, and a final decrease during contractions of greater force (177, 179-183). Although responses to TMS are affected by cortical and spinal excitability, a similar pattern of modulation is present for CMEPs amplitude when measured during contractions of different forces (179). This suggests that the main source of the modulation of MEPs amplitude with increasing force occurs at a spinal level (179). Specifically, this pattern of modulation seems to be related to how motor units are recruited during contractions of increasing force (179, 180, 182), with the latter decline in amplitude being related to a decrease in the responsiveness of the α-motoneurons firing at high rates (184, 185). During high firing rates, the trajectory of the afterhyperpolarization between spikes is more linear and the duration is shorter. The shorter duration of the time between spikes reduces the time that the membrane potential stays below threshold, reducing the time avaialable for excitation. The linear trajectory of the afterhyperpolarization makes that the membrane potential of the motoneuron stays far from the firing threshold a greater proportion of the time between spikes, reducing its probability of firing in response to new inputs compared with lower firing rates, in which the trajectory is more exponential.(185). This influence of α-motoneuron firing rate on MEP amplitude explains why the relation between MEP amplitude and contraction force depends on the muscle (179, 180, 182). In some muscles like the first dorsal interosseous, all motor units are recruited at low force levels and further increases

in force are attained by increasing their firing rate (186). In those cases, the peak amplitude of the MEP is reached at low forces, and further increases in force provoke a decrease in MEP as a consequence of the increase in the firing rate of the already recruited α-motoneurons (179). However, in those muscles in which new motor units are progressively recruited until greater levels of force, such as the biceps brachii (BB) (187), the MEP can continuously increase until contractions of around 75% of the maximal voluntary contraction (MVC), where it plateaus and start to decrease as a consequence of the increased firing rate of the already recruited α-motoneurons (179). In other muscles, like the soleus or the tibialis anterior, the MEP amplitude continuously increases with the force output, which suggests that new motor units are recruited even until near maximal force levels (180, 188).

Despite most of the modulation of the responses to TMS according to contraction force occurs at the spinal level, increases in the excitability of the cortical neurons projecting to the descending corticospinal neurons, or in the corticospinal neurons themselves, also influence the response to TMS (176, 178). This is supported, for example, by the large increase in the amplitude of the I-waves recorded at the cervical epidural space during maximal voluntary contractions (178). Furthermore, contraction force also influences the excitability of intracortical inhibitory and facilitatory circuits. SP duration is not affected by contraction intensity (141, 177), suggesting that the excitability of GABA-B inhibitory circuits is not affected by the level of force. This conclusion is reinforced by the lack of modulation of long-interval intracortical inhibition, another paired pulse TMS paradigm that measures the excitability of the same intracortical inhibitory circuits as SP (144). In contrast, SICI is progressively reduced according to contraction force (189-191), which seems to be related to a reduction in the inhibition of corticospinal neurons by inhibitory GABA-A circuits (144, 189, 191), and a concurrent facilitation of excitatory glutamatergic intracortical interneurons (190). It is believed that this modulation of intracortical excitatory and inhibitory circuits releases the cortical representation of the contracting muscle from inhibition, focusing the excitatory drive (192). Additionally, several studies using different techniques than TMS, such as brain imaging techniques (73, 114, 193), or recordings from single motor cortex neurons activity in non-human primates (194, 195), have shown that M1 activity is

correlated, although not totally in a linear way (196), to muscle activity and force. This suggests that M1 has an important role in controlling, among other kinematics variables such as position, velocity, or the direction of the limb; the force output during movements (194, 197).

Unilateral voluntary muscle contractions not only modulate the responses of the motor pathway controlling the contracting muscle, it also leads to changes in the response of the motor pathway projecting to the homologous contralateral muscle. Specifically, during unilateral contractions there is an increase in the amplitude of the MEPs in the resting contralateral homologous muscles according to the force of the muscle contraction (70, 112, 115, 181, 198-200). This facilitation of the MEPs obtained by TMS in the resting homologous muscles has been observed also in patients with agenesis of the corpus callosum (201). Therefore, it was initially proposed that the origin of this cross-facilitation was probably related to an increase in the α-motoneuron excitability of the resting homologous muscles (199-201). However, Hortobágyi et al. (70) found that strong unilateral wrist flexions increased the amplitude of the MEPs but not of the CMEPs in the contralateral resting wrist flexors. This data suggests that the facilitation of the MEPs in the contralateral homologous muscles occurs due to an increase in the excitability of the stimulated M1, without changes in the excitability of the α-motoneuron pool in the resting muscle (70).

Part of this increase in ipsilateral M1 excitability may arise from the concurrent activation of the ipsilateral sensory and motor cortical areas together with the contralateral hemisphere (71, 73, 114, 193, 202). Furthermore, as occurs with the contralateral hemisphere, this ipsilateral activation varies according to the force of the contraction (114, 193). The origin of this concurrent activation is not clear. The delay between the activation in the two hemispheres is in the millisecond range, therefore, a part of the activation is likely to occur simultaneously and inadvertently (203). However, there is a temporal element of this activation that is probably due to interhemispheric inputs acting on intracortical circuits in the ipsilateral hemisphere (203). Perez et al. (115) found that during unilateral contractions of increasing force there is a progressive release of GABA-A mediated intracortical inhibition (i.e. SICI) in the ipsilateral hemisphere. However, they also found a reduction in IHI from the active to the

resting hemisphere, supporting that the concurrent activation of the ipsilateral hemisphere is also influenced by interhemispheric interactions (115).

Another evidence about the influence of unilateral contractions on the motor pathway projecting to the resting homologous muscle is the presence of inadvertent muscle activity in the resting muscle (204-208). This activation is not always accompanied by overt movements but can be registered by EMG, usually called associated activity (208). As occurs with the cross-facilitation measured with TMS, the presence of associated activity is accentuated during strong unilateral contractions (206, 208-211). Although several theories have been proposed to explain the origin of the associated activity (212), like uncrossed corticospinal fibres coming from the hemisphere controlling the contracting muscle, it seems that associated activity arise from corticospinal input coming from the concurrent activation of the hemisphere ipsilateral to the contracting muscles (208, 211). Specifically it has been suggested that this associated activity may arise from the overload of a distributed cortical network responsible for restricting the motor output to the contralateral cortex, leading to a bilateral cortex activation (212-216).

2.2.2 Corticospinal modulation during fatiguing contractions

Although several definitions can be found over the literature, broadly fatigue refers to any reduction derived from exercise in the capacity of the neuromuscular system to produce muscle force (136, 217, 218). Muscle fatigue can be divided into peripheral and central fatigue (136). Peripheral fatigue refers to events occurring at or distal to the neuromuscular junction (217). Central fatigue refers to events occurring in the nervous system that lead to a failure or reduction in the ability to activate the muscle voluntarily (136, 217). The present section focuses on central fatigue and briefly describes the modulations in the corticospinal pathway controlling the exercising muscle and the contralateral resting homologous muscle during unilateral fatiguing exercise. Specifically, it focuses on the corticospinal modulation during sustained or repeated fatiguing muscle contractions due to its similarity with the exercise performed during RT sessions. Therefore, the effect of fatigue during whole body locomotor exercise or

corticospinal modulation during recovery of a fatiguing bout of exercise will not be discussed.

A MVC represents the maximal force ability of a subject, and is determined by peripheral factors, such as cross-sectional area of the muscle or group of muscles acting around a joint, and by the α-motoneuron output to those muscles (219). When a MVC is sustained in time, there is a fast progressive decline of around a 50% in the maximal torque in just 1-2 minutes (220-222). This fast reduction in voluntary maximal force is accompanied by a reduction in the amplitude of the EMG signal that occurs due to a reduction in the firing rate of the recruited α-motoneurons (217, 222, 223). This reduction in the α-motoneuron output occurs due to a combination of different factors. The amplitude of CMEPs is strongly reduced during a sustained MVC (224). This reduction suggests that a decrease in α-motoneurons excitability, probably due to a modification in their intrinsic properties (217, 224), has an important role in the decline in α-motoneuron output. However, other mechanisms may influence the α-motoneuron output, such as changes in neuromodulatory inputs that reduce the responsiveness of the α-motoneurons to ionotropic inputs (136, 217); or the modification in excitatory or inhibitory afferent inputs to the α-motoneurons, like for example a reduction in the α-motoneuron facilitation derived from IA afferent inputs (136, 225). However, during fatiguing maximal contractions, nervous system modulation is not restricted to changes at the spinal level. During a sustained MVC there is an increase in the MEPs amplitude despite the reductions in EMG amplitude (226, 227). This increase in MEPs, together with the decrease in CMEPs, suggest an increase in cortical excitability that may serve to counteract peripheral fatigue and reduced α-motoneuron excitability while trying to maintain the force output (217, 218). However, together with increased MEP amplitude there is a lengthening of the SP duration (220, 226, 228-230), suggesting also an increase of the efficacy of corticospinal inhibitory mechanisms which may contribute to fatigue. Together with those modulations in the excitatory and inhibitory balance, when TMS is superimposed during a sustained MVC there is a progressive increase in the force evoked by the magnetic stimulus (217, 218, 229-231). This increase in the response reflects a failure from supraspinal centers to harness the capacity of the muscle, probably due to a submaximal central output to the α-motoneuron (136, 218). When blood flow to a fatigued muscle after an

MVC is restricted by a tourniquet, which enhances the feedback from metabosensitive group III/IV muscle afferents, the suboptimal voluntary activation present during the MVC is maintained (220, 232). However, the modulations in MEP amplitude and SP duration return to baseline levels quickly despite the blood flow restriction (220). This suggests that the mechanisms limiting the supraspinal input to the α-motoneurons may be related to metabosensitive afferent input acting at other brain areas with inputs to the M1, but without affecting directly to motor cortical cells (218). Another possibility is that the input from the M1 to the α-motoneuron pool during the MVC is maintained but it is less effective to produce α-motoneuron output, with a part unexploded by the voluntary effort (i.e. not leading to α-motoneuron output) but that can be activated by the TMS, producing a muscle twitch (221).

During a sustained submaximal contraction in which subjects have to maintain the level of torque, EMG amplitude increases instead of the decline that occurs during a sustained MVC (217, 218). This different behaviour is probably related to the pattern of α-motoneuron recruitment. During an MVC, all α-motoneurons are recruited from the start and there is a progressive decline in their firing rate together with a derecruitment of the larger α-motoneurons (233, 234). However, during submaximal contractions, there is a decrease in the firing rate of the initially recruited α-motoneurons together with the recruitment of new ones (235-237). Furthermore, the latter recruited α-motoneurons increase their firing rate as the contraction continues, while the first recruited continue decreasing their firing rate or are even derecruited (237, 238). However, despite the dissimilarities in α-motoneuron recruitment, the effects of sustained submaximal efforts at the spinal and cortical level are similar to those present during an MVC (217). During submaximal contractions, there is also a reduction in α-motoneuron excitability (239). However, this reduction is greater in the early recruited low-threshold α-motoneurons, as suggest the greater reduction in the amplitude of small CMEPs, in which the contribution of the low-threshold α-motoneurons is larger due to the size principle (239). At the cortical level, there is an increase in the descending drive to recruit new α-motoneurons, as suggests the associated increase in EMG and MEP amplitude during torque matched sustained submaximal contractions (217, 240, 241). This is also supported by the increase in brain activation during submaximal sustained contractions found with brain

imaging techniques (71, 242). However, this increased drive also leads to supraspinal fatigue (measured during brief interspersed MVCs) (240, 241). In fact, during submaximal contractions, the contribution of supraspinal fatigue to the reduction in force generation is greater than with MVC (218).

As explained in the previous section, during unilateral contractions the ipsilateral "resting" motor areas are also activated concurrently with the contralateral ones. This ipsilateral activation is not only affected by contraction intensity, but also by the magnitude of fatigue of the contracting muscles (71). In fact, the ipsilateral activation during submaximal unilateral contractions rises progressively as fatigue in the contracting muscles develops (71). Part of this ipsilateral activation is likely to occur simultaneously with the contralateral activation due to inputs from areas upstream both M1s (203, 208). However, during unilateral fatiguing contractions, there is a reduction in the IHI from the main active hemisphere to the "resting" hemisphere that may also contribute to increase the bilateral activation (207). Probably consequence of this increased ipsilateral activation during fatiguing unilateral contractions, there is a progressive facilitation of the MEPs obtained in the contralateral homologous muscles. However, this increased facilitation is probably also enhanced by the inadvertent associated activity in the homologous muscle, which also increases as fatigue in the contracting muscles develops (207, 208, 243).

2.3 NEUROMUSCULAR ADAPTATIONS TO RESISTANCE TRAINING

2.3.1 Acute corticospinal responses to a single bout of resistance training

Motor practice leads to rapid increases in motor performance in the trained task, such as increased acceleration of a finger during ballistic contractions (244, 245), or increased tracking accuracy while following a template during visuomotor practice (31). This fast increase in motor performance is thought to be related to a use-dependent plasticity by which there is a strengthening of the connections between the specific cortical M1 neurons activated during the task (i.e. Long-term potentiation (LTP)) (246). This use-dependent plasticity allows the learning of specific patterns of muscle activation related with the practiced task (246, 247). Use-dependent plasticity can be measured with TMS (248). Indeed,

several studies have found that different types of motor practice lead to increases in cortical excitability, reductions in intracortical inhibition, and enlargements of the motor cortical representation of the trained muscles (31, 245, 249-251).

After RT, a type of motor practice, force increases occur after just a few sessions, well before any increase in muscle hypertrophy occurs (24, 252, 253). The origin of this early increase in maximal voluntary force is believed to arise from adaptations in the nervous system (15, 60, 62, 254). In fact, several studies have found adaptations at the spinal or cortical level after short-term RT (32-34, 40, 49, 51, 255) (see section 2.3.2.2). However, some have suggested that RT can be considered a type of motor skill in which performance improvements, as occur with other types of motor practice, are related to a learning process of the proper muscle activation patterns brought about by LTP-like mechanisms at the M1 (31, 256). Following this argument, several studies have used a single RT session model similar to the one used in motor learning contexts (31, 75-78, 257-264). This model allows to track the earliest central nervous system responses to RT, which have been suggested to be the trigger for long-term neural adaptations following repeated RT sessions (75, 77, 118).

The first study that used this model to test if one session of RT is accompanied by a use-dependent plasticity at the M1 similar to motor skill learning, was the one by Jensen et al. (31). They tested the effects of a single session of BB RT, and of a complex visuomotor task requiring a precise control of the elbow joint by BB contractions to track varying force traces. They found that only the subjects who performed the visuomotor tracking task experienced an acute increase in the MEPs obtained by TMS. This suggests that the initial force improvements after RT may not be related to a similar cortical plasticity process like the one involved in learning a new skill (31). However, the later findings by Selvanayagam et al. (75) showed a different picture. In this study the subjects performed RT protocols based on isometric wrist extensions. During RT the subjects contracted the wrist in a direction 90º deviated from the direction of the single pulse TMS twitches recorded before training. What the authors found is that RT shifted the direction of the muscle twitches evoked by single pulse TMS from the initial to the trained direction. In contrast with the study of Jensen et al. (31), these results suggest that RT leads to LTP-like mechanisms at the M1 that

strengthen the synapses of the corticospinal pathway, thus facilitating a muscle activation pattern of the wrist muscles in the trained direction (75).

Since those two seminal studies, several publications have delved on the acute corticospinal response to a single bout of RT (31, 75-78, 257-264). Results suggest that one session of RT leads to acute increases in CSE measured by TMS MEP amplitude (76-78, 258-260, 262, 263, 265), although the results do not always support this conclusion (31, 261, 263, 264). Regarding the SP accompanying the MEP, the results are mixed, with some studies finding decreases (78, 258, 260) or increases (264) after a RT session. Together with the increase in the MEP amplitude, some studies have also found a concomitant increase in the amplitude of the twitches evoked by single pulse TMS (75, 77). Muscle twitches are the sum of the forces produced by all the muscles acting around a joint activated by the non-focal single pulse TMS. Therefore, the acute increase in twitch amplitude suggests that one session of RT strengthens the corticospinal pathway projecting specifically to the trained muscle (75, 77). Some studies have also used paired pulse TMS paradigms to test possible changes in the efficacy of intracortical inhibitory or facilitatory circuits. However results are inconsistent, some authors report decreases in SICI (76, 258, 259, 262) and increases in ICF (258, 259, 262), but others do not (76, 78, 260, 261). At the spinal level, increases in α-motoneuron excitability or increases in the efficacy of corticospinal-motoneuronal synapse, may also contribute to increase single pulse TMS response, as suggest the acute increase in the amplitude of CMEPs (77). However, increased CMEP amplitudes after a bout of RT are not always present (257).

Therefore, despite inconsistencies, the overall results suggest that one RT session leads to increases in the response to single pulse TMS of the trained muscles. This increased TMS response may be related to an increased cortical or spinal excitability although changes in intracortical inhibitory or facilitatory circuits may also contribute. Part of the inconsistencies in the results between studies may be related to different measurement methodologies or even to the characteristics of the RT bout (265). For example, the type of contraction influences the acute response to RT (262). Eccentric contractions lead to a greater corticospinal modulation after a bout of RT than concentric contractions (262), which may be related to differences in the nervous system output between types of contraction (113, 171, 172, 266). It is likely that other training variables with

great influence on the nervous system output, like contraction intensity, also influence the acute response to a bout of RT (see section 2.2). Furthermore, the level of fatigue could also influence the acute corticospinal responses. In fact, some have suggested that these short-term modulations at the corticospinal pathway, may be a mechanism to counteract the neuromuscular fatigue developed during training rather than being related to motor learning processes (260, 262, 267).

As explained in the sections above, unilateral contractions do not only activate areas in the contralateral cortex, also ipsilateral brain areas (70, 71, 73, 112, 114, 115, 181, 193, 198-200, 202). Therefore this concurrent activation may act as a training stimulus in the untrained hemisphere, leading to long-term neural and functional adaptations in the untrained homologous muscles (i.e. CE) (18, 64, 66-69). However, as occurs with the trained side, some corticospinal modulations in the untrained hemisphere may occur after just one RT session. This topic will be addressed with more detail in the literature review presented in the chapter VI (111).

2.3.2 Chronic adaptations to resistance training

2.3.2.1 Functional adaptations to resistance training

Trained side

RT is one form of motor training widely used in sports performance (1-4), health (5-14), and recreational training programs. It basically consists on performing repeated dynamic (eccentric or concentric) or isometric muscle contractions against a load, usually distributed in groups of repetitions (i.e. sets) interspersed by rest periods. The main functional adaptations to RT are increases in the ability to produce maximal voluntary muscle force accompanied by muscle hypertrophy (15). Muscle force is the maximal ability to generate torque around a joint by the excitation of a muscle or a group of muscles, and it is influenced by the size and the physiological composition of the muscle and by the total output of the α-motoneurons to those muscles (219). Although there are several different methods to measure voluntary force depending on the devices used, the type of contraction, or the time to generate maximum force among other variables, the

most common tests used to quantify maximal voluntary force are the one repetition maximum (1RM) and the MVC (219). The 1RM is the greater amount of weight that can be lifted once in a specific RT exercise and informs about the maximum ability to generate concentric force (219). The MVC is used to measure the maximum isometric force and it requires to perform a maximum voluntary contraction against an immovable object connected to a force transducer, a device that measures the modifications in electrical resistance depending on the force applied while pushing (pressure) or pulling (tension) it (219). Changes in maximal voluntary force derived from RT are usually greater when the test used to measure it is equal or has similar characteristics to the exercise used during training (type of contraction, movement pattern, device, etc.) (268-270). However, RT is not only associated with increases in maximum voluntary force. RT is also usually associated, for example, with an increase in the ability to generate large amounts of force in less time (i.e. power) (271-274), which could be more relevant for sport performance or activities of daily living, where it is more usual to perform muscle contractions against submaximal loads (271, 275).

The other main adaptation to RT is the increase in muscle mass or hypertrophy (15). Hypertrophy is the consequence of a positive balance between protein synthesis over protein breakdown due to the great increase in protein synthetic rate occurring after a RT bout (276). This increased anabolism provokes an increase in muscle size mainly by an increment in the number of sarcomeres in parallel and noncontractile elements, including glycogen and fluid content (276). Muscle hypertrophy is usually quantified by measuring the change in cross-sectional area of the trained muscles using scanning techniques (e.g. magnetic resonance imaging, computerised tomography, ultrasound), biopsies to measure changes in muscle fibres cross-sectional area, or by estimating it with anthropometry (277-281). Significant increases in muscle mass are not observed until 3-6 weeks of RT, depending on the sensitivity of the technique used to measure it or the training stimulus (282-285). Therefore, it is thought that the early increase in voluntary force during the initial stages of a training period is related to neural adaptations (see next section), and muscle hypertrophy do not significantly contribute to increases in voluntary force until several weeks of RT (15, 26, 27, 252, 254).

The magnitude of adaptations in maximal voluntary force and muscle mass after RT varies in a wide range. For example, after 12 weeks of progressive dynamic RT, the response of 585 subjects ranged from 0 (no increases) to 250% increases in elbow flexors 1RM, or from -2% (decreases) to a 59% increase in the BB CSA (286). Part of the variability in the adaptations to an equal RT protocol between subjects can be partly explained by the influence of non-modifiable factors such as genetics (287), sex (286), age (288) or the training status of the trainees (289). However, in addition to these non-modifiable factors, there are numerous training variables that influence the adaptations to RT, such as training intensity (95-97, 290), fatigue (103-107, 291), training volume (98, 99, 292, 293) and frequency (101, 102, 294, 295), or the type of contraction (296-300). However, of those variables, the more relevant for the present thesis are the training intensity and the level of fatigue.

Training load, or training intensity, is usually determined by the weight of a constant external load lifted in a dynamic RT exercise, or by the quantity of force applied during an isometric contraction against or towards an immovable resistance. It is usually expressed in relation to the maximum voluntary force in a specific exercise as a % of the 1RM or the MVC. However, during dynamic RT exercises against a constant external load, it is also common to prescribe a number of repetitions that should be done with the maximum amount of weight that allow to reach this number of repetitions (e.g. 10RM load means the maximum weight that can be lifted 10 times) (301). Training load does not influence to a great extent the magnitude of hypertrophy when training volumes are matched and every set is performed until concentric muscular failure (i.e. the moment where no more concentric repetitions could be done due to fatigue) (96). It is likely that the similar muscle hypertrophy between load ranges is related to the increased motor unit recruitment that occurs during submaximal contractions to compensate for the decline in motor unit firing rate in the initially recruited motor units (see section 2.2). This increase in motor unit recruitment during fatiguing submaximal contractions leads to the recruitment of the full spectrum of type I and II motor units, even when using loads as low as 30% of the 1RM (302). This increased activation compensates for the differences in motor unit recruitment between training loads present at the beginning of a set, or when sets are not carried to muscle failure, leading to a similar training stimulus despite different

training loads (302). In contrast, training load is a determinant variable to maximize the increases in voluntary muscle force (96, 97). It is likely that differences in force adaptations between load ranges despite similar effect on hypertrophy are related to heavy-load RT inducing greater neural adaptations, such as increased voluntary activation (97).

The level of muscle fatigue during training has been also suggested to influence adaptations to RT (103-107, 291). The level of fatigue or level of effort during RT is usually controlled by the number of repetitions done in relation to the total amount of repetitions that can be done during each set (i.e. failure), or by the amount of velocity or power loss during a set compared to the initial or maximal value (103, 303-306). Sets to a number of repetitions close to the maximum that can be done, to concentric muscular failure, or to a greater % of power or velocity loss, lead to greater levels of fatigue (303, 307). Another form to manipulate fatigue during RT is to include brief rest periods between repetitions, which is generally known as "cluster training" (308, 309). Muscle fatigue has a profound influence on nervous system output and muscle properties (see section 2.2). The metabolic stress derived from exercise (i.e. the increase in exercise-induced metabolites such as inorganic phosphate or H+) is increased during fatiguing RT (276, 291). Some have suggested that this metabolic stress, together with the increase in motor unit recruitment that occur during submaximal contractions as fatigue develops (235, 302), is key to maximize RT adaptations (107, 291, 310). Therefore, fatiguing RT, such as RT to failure, has been suggested to be a superior training stimulus for strength and hypertrophy adaptations compared to less fatiguing RT (105, 107, 291, 311, 312). Indeed, muscle fatigue may be required to maximize hypertrophy and strength adaptations with low-load RT (313-315) due to the initial lower motor unit recruitment (174, 235). However, some evidence suggests that with high-load RT, fatigue is not a necessary stimulus to exploit maximal voluntary force adaptations (103, 104, 106). Therefore, it is usually recommended to limit fatiguing RT to short periods to reduce the risk of overtraining or injuries (276, 311, 312, 316).

Untrained side

When performed unilaterally while the other limb is at rest, RT produces not only increases in the maximal voluntary force of the trained muscles but also of the non-trained contralateral homologous muscles (18-22, 28, 108, 110, 317).

This phenomenon is known as CE. Since the first report by Scripture et al. (20) in 1894, CE has been the focus of many research efforts due to its potential as an adjuvant to rehabilitation programs for patients with unilateral weakness due to orthopaedic injuries or neurological disorders (79, 81, 318, 319). Although initial scepticism attributed CE just to a familiarization with the testing procedures (19), CE has been found also in properly randomized control trials in which there is a control group, which allows the exclusion of a familiarization effect as the underlying mechanism of CE (18, 19, 108, 110, 320). It is believed that CE arises from neural adaptations in the untrained hemisphere consequence of its concurrent activation during the unilateral contractions (see next section) (18, 64, 66-69). Indeed, several studies did not find any change in muscle mass of the untrained muscles even after training periods of 6-12 weeks (21, 23, 321), which reinforces the neural origin of CE.

The overall magnitude of CE is around a 12-18% according to the last two meta-analyses published (17, 18), a greater effect than reported before (~8%) (19, 68). CE has been measured in muscles of the upper (23, 28, 74, 110, 320, 322-325) and the lower limbs (28, 39, 55, 108, 317, 321, 326), however, untrained leg muscles seems to be slightly more benefited from unilateral RT (~16%) than upper limb muscles (~9%) (18). It has been suggested that CE occurs unidirectionally from the trained dominant limb to the untrained non-dominant limb, and not vice versa (323). However, there are studies that have found a CE effect in the dominant limb after non-dominant limb unilateral RT (327, 328), which suggest that CE of maximal voluntary force is indeed bi-directional and may not be influenced by laterality (327). Regarding the effect of the age of the trainees, the activation of the ipsilateral hemisphere during unilateral contractions is greater in older adults (329), which could mean a greater training stimulus for the untrained ipsilateral hemisphere, leading to a greater CE (see next section). However, CE of maximal voluntary force is similar in young and old adults (17, 330). Likewise, CE has been measured in men and women without differences between sexes (17, 286, 331). Nevertheless, a common factor of the participants in most of the studies, regardless of age or sex, is the lack of previous experience in RT, which could have enhanced the maximal voluntary force increases in the trained and the untrained limbs (18).

Training characteristics and testing procedures used to measure the force of the untrained limb also affect the magnitude of CE. CE has been observed after RT with isometric (325, 332, 333), concentric (108, 109), eccentric (108, 109, 320, 334) or a combination of concentric-eccentric contractions (39, 74, 327, 335-337). However, pure eccentric training (108, 109), or a combination of concentric and eccentric training (18), have a greater potential to induce adaptations in the untrained limb than pure concentric or isometric contractions. Nevertheless, independently of the type of contraction, CE is always higher when the test used to measure it resembles the exercise performed during training regarding to the type of contraction (108, 109), the position of the limb (338), or the angle of the joint during isometric RT (333).

Besides the type of contraction, other variables of the training protocol influence CE. For example, in a randomized controlled trial with 115 participants, a CE effect of a 7% was found after six weeks of unilateral RT in the group that performed three sets per session, but not in the group that performed just one set per session (110). This finding suggests that greater RT volumes enhance the adaptations in the untrained limb. In the same study, the authors also reported a tendency towards a greater CE when RT is performed at faster contraction speeds for the same external load (110). Related to the distribution of training days over time, a recent study compared the time course of CE between a traditional RT protocol, in which subjects trained three days per week for six weeks, with a group that performed one daily RT session for 18 consecutive days (i.e. the same total amount of training sessions) (339). CE after the first 15 sessions was similar for both groups, however, it occurred in significantly less time for the daily versus distributed RT group (i.e. two vs. five weeks, respectively). This means that CE may be accelerated by reducing the time interval between sessions when the focus is the untrained limb (339). This accelerated CE may be related to a greater amount of practice (i.e. volume) over the first two weeks (110).

As explained in the section 2.2, high contraction intensities (70, 112, 114, 115, 181, 193, 198-200), and high levels of fatigue (71), separately, lead to a greater concurrent activation of the untrained hemisphere. Because CE is thought to arise from adaptations in the untrained hemisphere consequence of its concurrent activation during unilateral contractions (18, 64, 66-69), training load and fatigue may influence CE (111). However, regarding training load, most of the studies

have used loads greater than a 50% of the maximum force in the trained exercise (18, 111). The few studies that have measured CE after low-load RT found inconsistent results, with increases (59), or no changes (340) after 3-4 weeks of unilateral RT. Therefore, how RT load affects CE is not clear. Because there is a positive correlation between force increases in the trained and the untrained limb (18), it could be expected that RT protocols leading to greater adaptations in the trained muscles also lead to greater CE. Therefore, greater RT loads are probably more effective than lower loads. However, from a practical point of view, it is relevant to know if low loads are also effective to produce CE, because rehabilitation programs, for which CE is though, usually include home-based exercises (341) where it could be difficult to use high RT loads for the stronger muscles. Therefore, more research is needed to determine the effect of RT load on CE. Regarding the effect of fatigue of the trained limb during unilateral RT on CE, only one study and a complementary study with a small sample size (n = 6) have addressed this question (42, 342). In each study the authors compared two protocols with the same load but leading to a different level of fatigue in the trained limb. One group performed a less fatiguing protocol in which each muscle contraction was separated from the next by ~18 seconds of rest (42, 342). This type of training has been associated whit low levels of fatigue and the maintenance of the power level during the whole training session (343). The other group performed a more traditional RT protocol in which all repetitions of every set were performed without rest, leading to a greater amount of fatigue (42, 342). However, the results are contradictory, with one study suggesting that more fatiguing protocols may enhance CE (342), while other do not (42). Therefore, more research is needed to determine the effect of fatigue in the trained limb during unilateral RT on CE of voluntary muscle force.

2.3.2.2 Neural adaptations to resistance training

Trained side

The development of maximal voluntary force is not only related to increases in muscle mass, but also to the ability to harness the full capacity of the contractile elements of the muscle through its activation by the nervous system. Therefore, it is believed that adaptations in the nervous system contribute to increase the

ability to voluntarily generate force (15, 26, 27, 60-62, 254, 256, 344, 345). Some indirect and direct evidence support this argument.

When a previously untrained subject starts a RT period, muscle force increases sharply during the first weeks of training (253). However, this early increase in voluntary force is not accompanied by muscle hypertrophy (25, 252, 321) or changes in the intrinsic ability of the muscle fibres to generate force, as suggests the lack of increase in the force of the twitches evoked by electrical stimulation of the peripheral nerve (30, 34, 47). This divergent time-course between peripheral changes and maximal voluntary force has been interpreted as an indirect evidence of the contribution of nervous system adaptations to force increases (26, 27).

Independently of the muscle properties, muscle force depends on the α-motoneuron output to the muscle, which is determined by α-motoneuron recruitment and the rate at which each recruited α-motoneuron fires (219). Therefore, any change in the nervous system contributing to increase maximal voluntary force has to produce an increase in the α-motoneuron output. This α-motoneuron output has been tried to be measured by several methods. The amplitude of the EMG signal during a maximal voluntary contraction has been one of the most used techniques to measure neural adaptations (62). This electrophysiological technique is used to measure the action potentials spreading along the sarcolemma of the muscle fibres under the electrodes (159, 346). Because, among other factors, EMG amplitude is determined by motor unit recruitment and the firing rate of the recruited motor units, it has been used as a surrogate of the α-motoneuron output to the muscle (159). Several studies have found an increase in EMG amplitude after RT, which has been interpreted as an increased α-motoneuron output (273, 321, 347-355). Also decreases in EMG amplitude of the antagonist muscles have been reported, suggesting reductions in antagonist co-activation during MVCs, which would increase the net torque towards the desired direction (351, 356). However, interpretation of changes in EMG after RT is complicated. EMG amplitude during a voluntary contraction is affected by several factors not related to the nervous system output, like changes in the position of the electrodes, muscle temperature, or anatomical changes (138, 159, 346, 357). The influence of these factors on the interpretation of changes in EMG amplitude after a period of RT can be reduced by normalizing its amplitude

with the M_{max} (see section 2.1) (138). However, even normalized EMG amplitude could be affected by changes in the intracellular action potentials provoked by peripheral factors, leading to misleaded conclusions about changes in the neural drive (358). Furthermore EMG signal can be underestimated by the cancellation of the action potentials that compose it, which further limits its potential as a measure of neural adaptation to RT (15, 346).

However, despite the limitations of EMG as an index of neural adaptations, other techniques support that RT increases the α-motoneuron output to the muscle. The twitch interpolation technique has been used to measure the voluntary activation, which is determined by the α-motoneuron output (136, 219, 359, 360). This technique consists in delivering a supramaximal electric stimulus to a peripheral nerve during a MVC (219). If the electric stimulus produces an increase in force during the MVC, it means that the superimposed stimulus was able to further increase the α-motoneuron output, suggesting a suboptimal voluntary activation. Although not consistently (359, 361), several studies have found that after a period of RT, there is a decrease in the superimposed force evoked by the electrical stimulus during the MVC (51, 362-368). This reduction in the superimposed force suggests that RT increases the α-motoneuron output during the MVC, leading to a greater voluntary activation. This increased voluntary activation may be related to changes in motor unit behaviour during voluntary contractions. Indeed, a novel study using high density EMG, a technique that allows to track specific motor units longitudinally, found that force increases after four weeks of RT were accompanied by a reduction in the recruitment threshold and an increase in motor unit firing rate during submaximal isometric contractions (255). This finding agrees with previous reports of increased motor unit firing rate during submaximal (369) and maximal contractions found with intramuscular EMG recordings after RT (253, 370). Those changes in α-motoneuron output to the muscle may be related to mechanisms leading to an increased responsiveness of the α-motoneurons to the same synaptic inputs, or to an increase in the magnitude of the synaptic inputs towards the α-motoneurons (255, 371).

Increased α-motoneuron excitability would increase the responsiveness to a synaptic input after RT. If an increase in α-motoneuron excitability due to RT is related to changes in their intrinsic properties, those changes should be apparent

when α-motoneuron responsiveness is measured at rest. However, several studies have found no changes in the H-reflex amplitude at rest (32, 49, 51, 53, 54, 62, 372). Although H-reflex amplitude is also affected by presynaptic inhibition of IA afferents (161), a recent study also found no changes in the amplitude of CMEPs at rest after four weeks of RT (47). Due to its monosynaptic nature (158), CMEPs are a better index of α-motoneuron excitability and the efficacy of the synapse between corticospinal neurons and α-motoneurons (153). Therefore, CMEPs and H-reflex data suggest that RT does not increase α-motoneuron excitability or corticospinal-motoneuronal synaptic efficiency, or decrease IA afferent presynaptic inhibition when measured at rest (62). However, there are some mechanisms that may specifically alter the responsiveness of α-motoneurons to an input during contractions. For example, serotonergic neuromodulatory inputs coming from the brainstem enhance α-motoneuron excitability and are particularly active during contractions (373, 374). Therefore, RT derived adaptations in the neuromodulatory inputs to the α-motoneuron pool may increase the α-motoneurons excitability during contractions. Indeed, some studies have shown an increased H-reflex amplitude during contractions, suggesting increased α-motoneuron excitability or decreased Ia afferent presynaptic inhibition (49, 53, 54). However, results are inconsistent (51, 362, 372) and a recent meta-analysis showed no effect of RT on H-reflex amplitude either at rest or during contraction (62). Therefore, overall results suggest that enhanced α-motoneuron output may not be related to an increased α-motoneuron responsiveness, but rather to an increased synaptic input towards them.

If an increase in the synaptic input is the mechanism leading to a greater α-motoneuron output, allowing a better harness of the muscle force capabilities, it should be apparent during maximal voluntary contractions. The V-wave obtained during MVCs, considered a proxy of the descending drive to the α-motoneurons (49) (see section 2.1), increases after RT (49, 51, 54, 57, 62, 372). However, the extra drive towards the α-motoneurons after RT that allows the V-wave to increase, may be related not only to a greater corticospinal input, but also to an increased contribution of reflex inputs during the voluntary contraction due to a decrease in presynaptic inhibition, for example (60, 375). Notwithstanding, although not always (36), short-term RT increases voluntary activation measured with TMS, which suggests an enhancement of the initially suboptimal supraspinal input to

the α-motoneuron pool (47). Those increases in the supraspinal input may be related to adaptations at the M1, or in other areas that influence the M1 output during maximal force production (60).

A recent meta-analysis found that, although not consistently over the literature (36, 39, 44, 327), MEPs amplitude obtained during contraction increases after a period of RT (33, 38, 40, 44, 45, 62, 376, 377). In the same line, the force of the TMS-evoked twitches of the trained muscles also increase after RT (34). Although the response to TMS is also affected by changes at the spinal level, the lack of consistency in the effects of RT on the responsiveness of α-motoneurons, suggests that increases in the responses to TMS may be related to changes in the excitability of cortical and corticospinal neurons projecting to the trained muscles. Cortical and corticospinal excitability increases may be related not only to changes in the neuron's membrane properties, but also to adaptations in the intracortical inhibitory or facilitatory circuitry projecting to them (see section 2.2). Indeed, it has been shown that RT reduces GABA-A (i.e. SICI) (40, 44, 62, 335) and GABA-B (i.e. SP) (37, 39, 41, 45, 62) receptor-mediated intracortical inhibition. All those adaptations would hypothetically aid to increase the magnitude and the efficacy of the descending motor command to increase the α-motoneuron output, thus enhancing voluntary force production. Besides results derived from stimulation techniques, studies using brain imaging techniques have also found structural and functional brain adaptations after RT (23, 378). For example, one study found an increased mean diffusivity of the left corticospinal tract after 16 sessions of RT together with an increase in force, suggesting an increase in myelination of the corticospinal tract (378). Also functional magnetic resonance imaging techniques have shown an increase in the activation of the M1 among other brain areas after RT (23), although this increased activation may not necessarily be functionally related to force enhancements (60).

Therefore, overall results suggest that short periods of RT lead to an increased voluntary force paralleled with increased motor unit firing rate (255). Those increases in α-motoneuron output are mainly related to an increased corticospinal input to the α-motoneuron pool, which may be linked to functional and structural adaptations at supraspinal sites (47, 62). However, adaptations at the spinal level increasing the responsiveness of the α-motoneuron pool to synaptic inputs cannot be discarded.

Untrained side

As occurs with the trained muscle, an increase in muscle force in the absence of muscle hypertrophy has been interpreted as an evidence of neural adaptations leading to the increases in voluntary force production (26). However, in contrast with the trained side, where increases in muscle mass may contribute to increase maximal voluntary force after the initial 3-6 weeks of training (282-285), in the untrained homologous muscles hypertrophy does not occur even after longer training periods (21, 23, 321). Therefore, CE has been ascribed totally to neural factors (63).

Two main theories have been proposed to explain the neural mechanisms underlying the increase in performance of the untrained limb after a unilateral task (66, 67). The "bilateral access" hypothesis suggests that the improved motor engrams related to a proper execution of the trained task derived from practice with the trained limb, may be accessed by the untrained hemisphere, leading to an increase in performance in the untrained limb (66, 67). This theory has been more accepted for intermanual transfer of motor tasks like serial reaction time tasks. However, with regards to CE of maximal voluntary force, the most widely accepted theory is the "cross-activation" hypothesis (66, 67). As explained in section 2.2, during unilateral contractions several areas in the ipsilateral hemisphere are also activated (70, 71, 73, 112, 114, 115, 181, 193, 198-200, 202). The cross-activation hypothesis suggest that the repeated activation of those areas during unilateral RT serves as the stimulus for the untrained hemisphere, leading to permanent functional adaptations (66, 67). Both theories are not mutually exclusive, and both assume a key role for the untrained hemisphere in the improvement of performance of the untrained limb.

In relation to the role of the untrained hemisphere regarding CE, Lee et al. (379) found that after four weeks of unilateral RT, CE was accompanied by an increase in the cortical voluntary activation of the untrained wrist extensors. These results suggest that CE may arise from an increased capacity of the untrained M1 to drive the corticospinal pathway projecting to the untrained homologous muscles (379). As occurs with the trained hemisphere, increases in the supraspinal input from the untrained hemisphere may be related to adaptations at the M1, or in areas that influence its input during maximal contractions (60).

At the untrained M1, the effects of unilateral RT on M1 excitability are contradictory, with studies showing increases (74, 89, 109, 325, 335-337) and no changes (39, 109, 327, 332, 336). In this regard, a recent meta-analysis reported no significant increases in the MEP amplitude obtained by TMS stimulation of the untrained hemisphere (63). As discussed in the literature review of the present thesis, inconsistencies in the results can be related to different measurement methodologies and different characteristics of the training protocols that may influence adaptations (see Chapter VI) (111, 380). However, as explained in the section 2.2, unilateral contractions do not only raise cortical excitability of the untrained hemisphere but also reduce the efficacy of intracortical inhibitory circuits in the M1 (115). Therefore, it may be reasonable that repeated unilateral contractions during RT may lead to chronic changes in the efficacy of those circuits. In this regard, several studies have found a reduction in GABA-A (i.e. SICI) (63, 109, 335, 336) and GABA-B (i.e. SP) (39, 63, 109, 327, 337) receptor-mediated intracortical inhibition in the untrained hemisphere after unilateral RT. Reductions in intracortical inhibition may improve the efficacy of the motor command to drive the untrained muscles, leading to CE.

Increased cortical drive to the untrained muscles could also be related to adaptations in areas other than the untrained M1, but with influence on its output. In this regard, Hortobágyi et al. (325) found that CE after eight weeks of RT is related to a decrease in the IHI from the trained to the untrained hemisphere. In the same study, they also found a correlation between CE and the increase in the MEP amplitude obtained by TMS of the untrained hemisphere during contractions of the trained muscle (325). An increase in the cortical excitability of the untrained hemisphere during contraction of the trained limb, rather than explain a mechanism by which the untrained hemisphere would increase its output during contractions of the untrained muscle, suggest that with chronic unilateral RT there is an increase in the concurrent activation of the untrained hemisphere during unilateral contractions. This increased concurrent activation would mean a greater training stimulus for the untrained hemisphere, thus explaining the significant correlation with CE (325). Therefore, the reduction in IHI could have contributed to CE actively, by releasing the untrained hemisphere from the inhibition of the trained hemisphere and increasing its ability to drive the untrained muscles during maximal contractions; or passively,

by allowing a greater untrained hemisphere concurrent activation during RT, which would enhance the training stimulus for the adaptations causing CE (325). Adaptations in other areas than the ones that can be tested with TMS can also contribute to CE. For example, Farthing et al. (23) found that after six weeks of RT, unilateral contractions of the untrained limb were associated with an increase in the activation of the temporal lobe of the trained hemisphere and of the untrained sensorimotor cortex. An increase in the activation of the trained temporal lobe, an area related to memory retrieval of prior movements (23, 381), may influence the output of the untrained M1 through interhemispheric interactions, which would be in agreement with the "bilateral access" theory (23, 66).

Changes at the spinal level that increase the responsiveness of α-motoneurons would also increase the output to the untrained muscles, thus contributing to CE. However, acute studies have shown that, in contrast with the increase in cortical excitability of the ipsilateral hemisphere during unilateral contractions, α-motoneuron excitability and presynaptic inhibition of the resting homologous muscles no change or increase, respectively (70). These acute studies suggest subtle modulations of the spinal pathway projecting to the resting homologous muscles, which agrees with the lack of change in the H-reflex of the untrained muscles after a period of unilateral RT (55, 326). Therefore, results suggest that CE is not mediated by changes at the spinal level of the pathways projecting to the homologous untrained muscles.

III - OBJECTIVES

III - OBJECTIVES

STUDY 1:

- To determine the effects of acute resistance training load on the electromyographic responses and twitch forces evoked by transcranial magnetic and electric corticospinal tract stimulation on the trained biceps brachii.

STUDY 2:

- To systematically review the literature to determine the effects of the type of muscle contraction, training load, degree of fatigue and external pacing of muscle contractions during unilateral resistance training on the acute responses and chronic adaptations of the untrained hemisphere.
- To detect the training variables in whose there is a lack of direct evidence about the effect of their modification on the acute responses and chronic adaptations in the untrained hemisphere.

STUDY 3:

- To determine the effects of acute unilateral resistance training load on the electromyographic responses evoked by transcranial magnetic stimulation on the trained and untrained BB.
- To determine if the increases in corticospinal excitability after one session of resistance training are related to changes in intracortical circuits.

STUDY 4:

- To determine the effects of load during four weeks of unilateral resistance training on the magnitude of cross-education and the neural adaptations in the trained and the untrained leg extensors.

- To determine the effects of the degree of fatigue developed during the sets during four weeks of unilateral resistance training on the magnitude of cross-education and the neural adaptations in the trained and the untrained leg extensors.

IV – HYPOTHESIS

IV - HYPOTHESIS

STUDY 1:

- Acute responses to transcranial magnetic and electric corticospinal tract stimulation will increase in an intensity-dependent manner in the trained biceps brachii after a bout of unilateral resistance training.

STUDY 2:

- Training load, type of contraction, the degree of muscle fatigue and the strategy of pacing the movement during unilateral resistance training will affect the acute responses and chronic adaptations in the untrained hemisphere. Specifically, we hypothesize:

o Eccentric contractions will enhance untrained hemisphere acute responses and chronic adaptations to unilateral resistance training compared to isometric or purely concentric contractions.

o Training load will affect untrained hemisphere adaptations in a load-dependent manner.

o Greater levels of muscle fatigue during the set will enhance untrained hemisphere acute responses and chronic adaptations to unilateral resistance training.

o Externally pacing the movement during resistance training will enhance untrained hemisphere acute responses and chronic adaptations compared to self-paced movements.

STUDY 3:

- Unilateral resistance training will increase the corticospinal excitability of the trained and the untrained biceps brachii in an intensity-dependent manner.

- Acute increases in corticospinal excitability of the trained and the untrained BB will be associated with concomitant decreases in intracortical and corticospinal inhibition, and increases in intracortical facilitation.

STUDY 4:

- High-load resistance training and higher levels of fatigue will enhance neuromuscular adaptations in the untrained side.

- High-load resistance training but not higher levels of fatigue will enhance neuromuscular adaptations in the trained side.

- Maximal voluntary force improvements in the trained and the untrained leg will be accompanied by increases in corticospinal excitability.

V – STUDY 1

V – STUDY 1:

Contraction intensity-dependent variations in the responses to brain and corticospinal tract stimulation after a single session of resistance training in men

5.1 ABSTRACT

The aim of this study was to determine the effects of acute RT intensity on MEPs generated by TMS and on CMEPs produced by electrical stimulation of the corticospinal tract. In four experimental sessions, 14 healthy young men performed 12 sets of eight isometric contractions of the elbow flexors at 0 (Control session), 25, 50 and 75% of the MVC. Before and after each session, MEPs, CMEPs, and the associated twitch forces were recorded at rest. MEPs increased by 39% ($P < 0.05$ vs. 25% and control condition, ES = 1.04 and 1.76 respectively) after the 50% session and by 70% ($P < 0.05$ vs. all other conditions, ES = 0.91 - 2.49) after the 75% session. In contrast, CMEPs increased similarly after the 25%, 50%, and 75% sessions with an overall increase of 27% ($P < 0.05$ vs. control condition, ES = 1.34). The amplitude of the M_{max} was unchanged during the experiment. The MEP- and CMEP-associated twitch forces also increased after RT, but training intensity affected only the increases in MEP twitch forces. The data tentatively suggest that the intensity of muscle contraction used in acute bouts of RT affects cortical excitability.

5.2 INTRODUCTION

RT is widely used to improve MVC force and muscle mass. However, the mechanisms underlying the increases in MVC force following mechanical loading of healthy skeletal muscle remain incompletely understood. Because MVC force increases after a few sessions of RT, before functionally meaningful muscle hypertrophy could occur, the initial adaptations leading to this rapid increase in MVC force are probably of neural origin (24, 49, 252, 253). Indeed, a variety of forms of motor practice can cause rapid adaptations in central nervous system (75, 77, 244, 245, 260, 382-384). Therefore, the acute changes in the central nervous system after a single session of RT (75-77, 260, 383) could act as a trigger for long-term adaptations following repeated training sessions.

This trigger could be an increase in the efficacy of the corticospinal-motoneuronal synapses, and increases in α-motoneuron and/or cortical excitability. In fact, a single session of isometric RT of the elbow flexors increased the size of MEPs and CMEPs measured at rest by TMS of the M1 and electrical stimulation of the corticospinal tract, respectively (77). CMEPs are affected by peripheral excitability, the efficacy of the corticospinal-motoneuronal synapses and α-motoneuron excitability, while MEPs are also affected by the excitability of motor cortical neurons. Furthermore, the amplitude of the twitch forces evoked by TMS and electrical cervicomedular stimulation also increased after a session of RT (77). Those involuntary contractions are the sum of the forces produced by different muscles activated by the same non-focal stimulus. Therefore, these increases in twitch forces towards the trained direction, together with the rise in the amplitude of MEP and CMEPs, suggest that a single session of RT preferentially strengthens the corticospinal-motoneuronal pathway projecting to the trained muscle (77).

The effects of different forms of motor practice on CSE can still be present up to an hour after the session (244, 385-388) and 25 minutes after RT (77). This lasting increase in CSE has been interpreted as a marker of use-dependent corticomotor plasticity probably mediated by mechanisms similar to long-term potentiation (385, 386).

Most acute RT studies have used high-intensity muscle contractions as an exercise stimulus. However, low- compared to high-intensity (96) RT can also improve MVC force, albeit to a lesser extent. Because the hypertrophy response to RT seems to be independent of intensity, the differences in the increases in MVC force brought about by low- and high-intensity RT may be related to differences in neural adaptations.

Contraction intensity affects the magnitude of corticospinal tract activation (73, 179, 181, 389). At the spinal level, stronger contractions intensities implicate higher motoneuronal excitability through pre-and postsynaptic mechanisms, increased motor unit recruitment and higher firing frequencies (235). This leads to an increase in CMEP amplitude with contraction intensity until a decrease during very strong contractions, which is proposed to relate to α-motoneuron afterhyperpolarization trajectory (179). Similar to CMEP amplitude, MEP amplitudes also increase with contraction intensity (179, 181, 389), even though such responses to TMS tend to saturate and may even decrease before reaching 100% of MVC force (179, 390). Spinal mechanisms (increased α-motoneuron pool excitability) could account for the increase in MEP amplitude, however the intensity of the contraction also influences the cortical output neurons and interneurons involved in generating the descending commands, as shown by neuroimaging studies and direct epidural recordings (73, 178). Additionally, the GABAergic mediated intracortical inhibition progressively decreases with the intensity of the contraction (190). It is thus conceivable that high- compared with low-intensity RT has a greater potential to induce neural adaptations. Whether the lasting effects on corticospinal and spinal α-motoneurons occur in a dose-dependent manner after a single RT session using low skill, invariant isometric muscle contractions, are unknown.

Therefore, the purpose of the present study was to determine the effects of acute RT intensity on the EMG responses (MEPs, CMEPs, M_{max}) and twitch forces evoked by brain and corticospinal tract stimulation. We administered all tests at rest to control for α-motoneuron excitability and because measurements at rest are sensitive to RT-induced changes in the central nervous system (77). We compared these outcomes for up to 30 min following RT at 25%, 50%, and 75% MVC, and a control resting condition (CON). We hypothesized that MEPs,

CMEPs, and the associated twitch forces would increase in an intensity-dependent manner after a bout of RT.

5.3 MATERIAL AND METHODS

5.3.1 Participants

Healthy, right-handed, and recreationally active men (2-3h per week of recreational sports activities or aerobic training, age, 23.5 ±3.93 years, n = 16) without contraindications to TMS and currently not taking any medications, participated in the study. Data from two participants were excluded from the analyses because it was not possible evoke CMEPs with a constant latency > 7.5ms. Participants came to the laboratory one week before the start of the experiments to become familiar with the MVC task, peripheral nerve stimulation, TMS, and corticospinal tract stimulation. Participants were asked to refrain from consuming caffeinated or alcoholic drinks and exercising 24 h before each testing session. The Institutional Review Board approved the protocol and the informed consent form, which all participants signed before the start of the experiments. The study was conducted in accordance with the latest version of the declaration of Helsinki.

5.3.2 Set-up

Participants were seated in a chair in front of a table with the right shoulder flexed at ~90º and the elbow flexed with forearms vertical (Fig. 1A). Right forearm was supinated and strapped at the wrist to a force transducer (NL63-200 Kg; Digitimer, Welwyn Garden City, United Kingdom) that measured voluntary and evoked twitch forces. The left arm rested on the table during the experiments. Visual feedback of voluntary elbow flexion force was displayed on a computer screen in front of the participant.

EMG activity was recorded from the right and left BB using Ag-AgCl surface electrodes (5-8 cm inter-electrode distance) attached to the skin with a belly-tendon montage. EMG signals were amplified (x200 to x300), band pass filtered (10-1000 Hz) and sampled at 2 kHz with a Digitimer d440 isolated

amplifier (Digitimer, Welwyn Garden City, United Kingdom). Force recordings were band-pass filtered (5-2500 Hz), amplified (x2500), and sampled at 2 kHz using a Neurolog System (Digitimer, Welwyn Garden City, United Kingdom). Both EMG and force signals were simultaneously collected using an analog-digital board CED Micro1401-3 (Cambridge Electronic Design, Cambridge, UK) for further analysis.

5.3.3 Brachial Plexus stimulation

M_{max} of the right BB was obtained via single electrical stimuli delivered to the right brachial plexus (200-μs duration, DS7AH constant current stimulator; Digitimer, Welwyn Garden City, United Kingdom). The cathode (pre-gelled Ag-AgCl electrodes) was positioned in the supraclavicular fossa and the anode on the acromion. Stimulation intensity (Range 40 - 168 mA) was set to 120% of what was needed to produce the M_{max} in right BB. A supramaximal stimulus was used to reduce the probability that some axons would remain inactivated because of axonal hyperpolarization due to fatigue (138). Twitch forces associated with each M_{max} were also recorded.

5.3.4 Transcranial Magnetic Stimulation

We generated MEPs in the right BB by placing a figure of eight coil (70 mm diameter; stimulator: DuoMag, Rogue Resolutions Ltd., UK) over an optimal spot of the left M1. The optimal site was obtained by exploring the estimated center of the BB motor cortical representation (4-7 cm lateral to the vertex). The hot spot, i.e., where a known supra-threshold intensity produced the largest responses, was marked on the scalp with a permanent marker. The coil was oriented with the handle pointing backward and laterally at around 45º to the midline. The stimulation intensity (58% - 100%) that induced an MEP of ~2-5% of the M_{max} amplitude, was determined at rest and used to test the effects of acute RT on CSE. Such a measure is sensitive to RT-induced neural adaptations (77). Peak twitch forces associated with MEPs were also recorded.

5.3.5 Electrical stimulation of the corticospinal tract at the cervicomedullary junction

Motor responses of the right BB were also obtained by electrically stimulating the corticospinal axons at the cervicomedullary junction. Pre-gelled Ag-AgCl electrodes were affixed over the left (cathode) and right (anode) mastoid process. Stimulation intensity (90 – 226 mA, 200-μs duration) was set to produce a CMEP of 10-20% of M_{max} with the right BB at rest. Such a measure is sensitive to adaptations in α-motoneuron excitability or the efficacy of the corticospinal-motoneuronal synapses induced by RT (77). Peak-to-peak twitch forces associated with each CMEP were also recorded.

5.3.6 Experimental procedures

5.4.6.1 Main experiment

Each subject completed four experimental sessions separated by 5-7 days in a random order: isometric RT at 0%, 25%, 50%, and 75% of MVC. The 0% or control session consisted of 20 min of sitting at the table used for RT.

Training consisted of 12 sets of eight, slowly ramped isometric contractions of the elbow flexors with four seconds of rest between contractions and one minute of rest between sets. Marked by a 2-s-long window, participants ramped up force to 25%, 50% or 75% of MVC represented by a horizontal line displayed on a monitor and relaxed as soon as they reached the target force at the end of the two seconds period (see Fig. 1B). The rate of force development was thus different between sessions.

During each session, participants performed three measurements blocks involving noninvasive stimulation 15, 10 and five minutes before RT. Immediately after RT, participants performed one measurement block (POST-0') that was repeated 5, 10, 15, 20, 25, and 30 min after POST-0'. The number of stimuli in each block was identical to a protocol reported previously (77): with two initial M_{max} measurements, five CMEPs and five MEPs elicited in a random order with both arms at rest. EMG of both BBs was monitored and participants were repeatedly reminded to relax both arms.

After PRE measurements and before each intervention, all participants performed 2-3, 3-5-s-long isometric elbow flexion MVCs with 90 seconds of rest between trials. The highest value of all the attempts was used to determine the training intensity for that session.

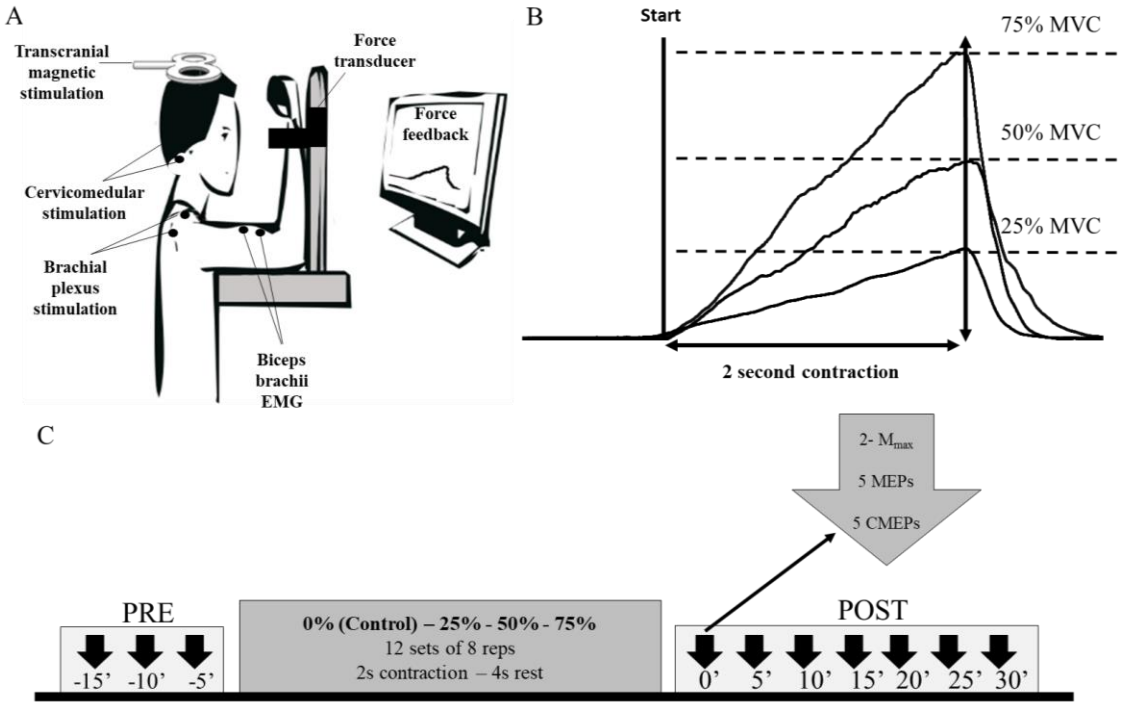

Figure 1. Schematic view of the set-up and protocol. (A) Participants completed the experiment comfortably seated with the elbow and the shoulder flexed to 90º in front of a screen showing the force feedback. (B) Raw traces of a contraction from each training session from a representative subject. In each training session the time in which participants have to steadily contract was identified with two vertical bars and the intensity required was marked with a horizontal line. (C) Motor evoked potentials and associated twitches were obtained before (PRE) and after (POST) each training (at 25, 50 or 75% of MVC) or control session (20 min of rest).

5.3.6.2 Complementary experiment

While contraction intensity differed between sessions (25, 50, 75% of MVC) each session comprised 12x8, i.e., 96 contractions. Thus, the total amount of physiological work performed differed between sessions. In a complementary experiment we therefore examined the effects of the exercise volume on measures of neural adaptations. Participants (n = 8) performed an additional session at 25% of MVC but with twice the volume used in the main experiment (i.e. 2 x 12 = 24 sets). Thus, the total amount of physiological work corresponded to work produced in the 50% session.

5.3.7 Data analysis

We measured the peak-to-peak amplitudes of M_{max}, MEPs, and CMEPs and MEPs and CMEPs were normalized to M_{max} within each measurement block and averaged. PRE measurements were represented as the average of all responses obtained in the three PRE blocks (i.e.: PRE -15, -10 and -5 min). We also measured the peak-to-peak twitch force amplitudes by calculating peak to peak values over a 200 ms time window after the stimulation.

To assess neuromuscular performance, we averaged the root mean square amplitude of the EMG activity (EMG_{RMS}) (normalized for M_{max} recorded in each session) and the impulse (force x time) within each of four 500-ms-long window (from 0 to 2 sec; i.e.: 0-0.5; 0.5-1; 1-1.5; 1.5-2 sec) during every two-seconds contraction.

5.3.8 Statistics

Normality was confirmed using the Kolmogorov-Smirnov test. Intra-session and inter-session reliability for M_{max}, MEPs, CMEPs, their associated twitches and stimulation intensities, was determined using intra-class correlation coefficients (ICCs) with 95% confidence intervals (95% CIs) from the mixed-effect model. The ICC was interpreted with values below 0.5, 0.5 to 0.75, 0.75 to 0.90, and > 0.90 indicating, respectively, low, moderate, good, and excellent reliability (391). To analyze neuromuscular performance during each training session, a two-way

repeated measures analysis of variance (RM-ANOVA) was performed with SET (1-12) and INTERVAL (1st, 2nd, 3rd, 4th) as factors for the EMG_{RMS} and the impulse (force area under the curve). A one-way RM-ANOVA with intensity as factor was performed for PRE-test measurements for M_{max}, MEPs, CMEPs and their associated twitches to detect any between-group differences at baseline. Because there were no between-group differences in the baseline values, the subsequent analyses were performed with each session data normalized to its PRE values (i.e., on the Pre- to Post-trial change scores). A two-way RM-ANOVA was performed with TIME (Pre, POST-0', POST-5', POST-10', POST-15', POST-20', POST-25', POST-30') and INTENSITY (CON, 25%, 50% and 75%) as factors for the M_{max}, MEPs, CMEPs and their associated twitch forces (all normalized to PRE values). For the complementary experiment, a two-way RM-ANOVA was performed with TIME (PRE, POST-0', POST-5', POST-10', POST-15', POST-20', POST-25', POST-30') and VOLUME as factor (25% and 25%x2) for M_{max}, MEPs, CMEPs and their associated twitch forces. The main effect of INTENSITY or VOLUME was also analyzed independently of the other main effects or interactions in order to detect the overall effect of every session on each variable during the 30 minutes post intervention. If sphericity was violated (Mauchly's test), degrees of freedom were corrected by Greenhouse-Geisser estimates of sphericity. Bonferroni correction was applied for post hoc analyses to account for multiple comparisons. Effect sizes are presented as partial eta square values (η_p^2; small: 0.02; medium: 0.13; large: 0.26) (392). Unless indicated otherwise, data are reported as mean ±standard deviation. SPSS 20.0 software (SPSS, Chicago, Illinois) was used for statistical analysis. Statistical significance was set at $P \leq 0.05$.

5.4 RESULTS

5.4.1 Main Experiment

Reliability — Intra-session reliability of M_{max}, MEPs, and CMEPs and the associated twitches was good to excellent (ICC = 0.88 to 0.99, Table 1). Inter-session reliability for M_{max}, MEPs, and CMEPs and the associated twitches and stimulation intensities was moderate to excellent (ICC = 0.67 to 0.98 Table 1).

Table 1. Mean PRE values for Mmax, MEP/Mmax and CMEP/Mmax and its associated twitches (mean ±SD) and intra-session and inter-session reliability.

	Session	**Pre value**	**Intra-Session ICC (95% CI)**	**Inter- session ICC (95% CI)**
M_{max} (mV)	CON	5.99 ± 1.60	0.99 (0.97, 0.99)	0.97 (0.93, 0.99)
	25	6.14 ± 1.59	0.99 (0.97, 0.99)	
	50	5.84 ± 1.52	0.99 (0.99, 0.99)	
	75	5.90 ± 1.78	0.99 (0.99, 0.99)	
MEP/M_{max} (% M_{max})	CON	5.59 ± 2.54	0.90 (0.76, 0.97)	0.93 (0.87, 0.97)
	25	4.26 ± 1.87	0.94 (0.84, 0.98)	
	50	5.69 ± 4.35	0.93 (0.84, 0.98)	
	75	4.57 ± 2.31	0.93 (0.84, 0.98)	
CMEP/M_{max} (% M_{max})	CON	11.29 ± 5.12	0.82 (0.57, 0.94)	0.67 (0.33, 0.88)
	25	10.93 ± 7.35	0.96 (0.91, 0.99)	
	50	10.66 ± 5.55	0.95 (0.88, 0.98)	
	75	9.87 ± 5.07	0.88 (0.72, 0.96)	
M_{max}-$_{twitch}$ (N)	CON	27.29 ± 7.79	0.96 (0.91, 0.99)	0.94 (0.89, 0.98)
	25	29.53 ± 10.79	0.96 (0.91, 0.99)	
	50	33.86 ± 8.81	0.96 (0.91, 0.99)	
	75	31.56 ± 12.42	0.99 (0.97, 0.99)	
MEP-$_{twitch}$ (N)	CON	2.36 ± 1.08	0.96 (0.90, 0.99)	0.95 (0.91, 0.98)
	25	2.34 ± 1.38	0.94 (0.85, 0.98)	
	50	2.55 ± 1.52	0.98 (0.95, 0.99)	
	75	1.87 ± 0.98	0.95 (0.88, 0.98)	
CMEP-$_{twitch}$ (N)	CON	6.43 ± 2.92	0.97 (0.94, 0.99)	0.91 (0.82, 0.97)
	25	6.21 ± 2.20	0,98 (0,94, 0,99)	
	50	6.07 ± 2.89	0.93 (0.83, 0.98)	
	75	5.59 ± 2.15	0.96 (0.89, 0.98)	

PRE values are expressed as means (SD). CI, confident interval; CMEP, cervicomedullary motor evoked potential; ICC, intraclass correlation coefficient; M_{max}, maximal compound muscle action potential; MEP, motor-evoked potential.

Neuromuscular performance — The two-way RM-ANOVA revealed that force impulse increased linearly from the beginning to the end of the contraction for all the intensities (Fig. 2A). Furthermore, the impulse remained unaltered across the sets. EMG activity normalized with the M_{max} of each session, increased linearly from the beginning to the end of the contractions for each set and intensity and remained stable across the sets (Fig. 2B).

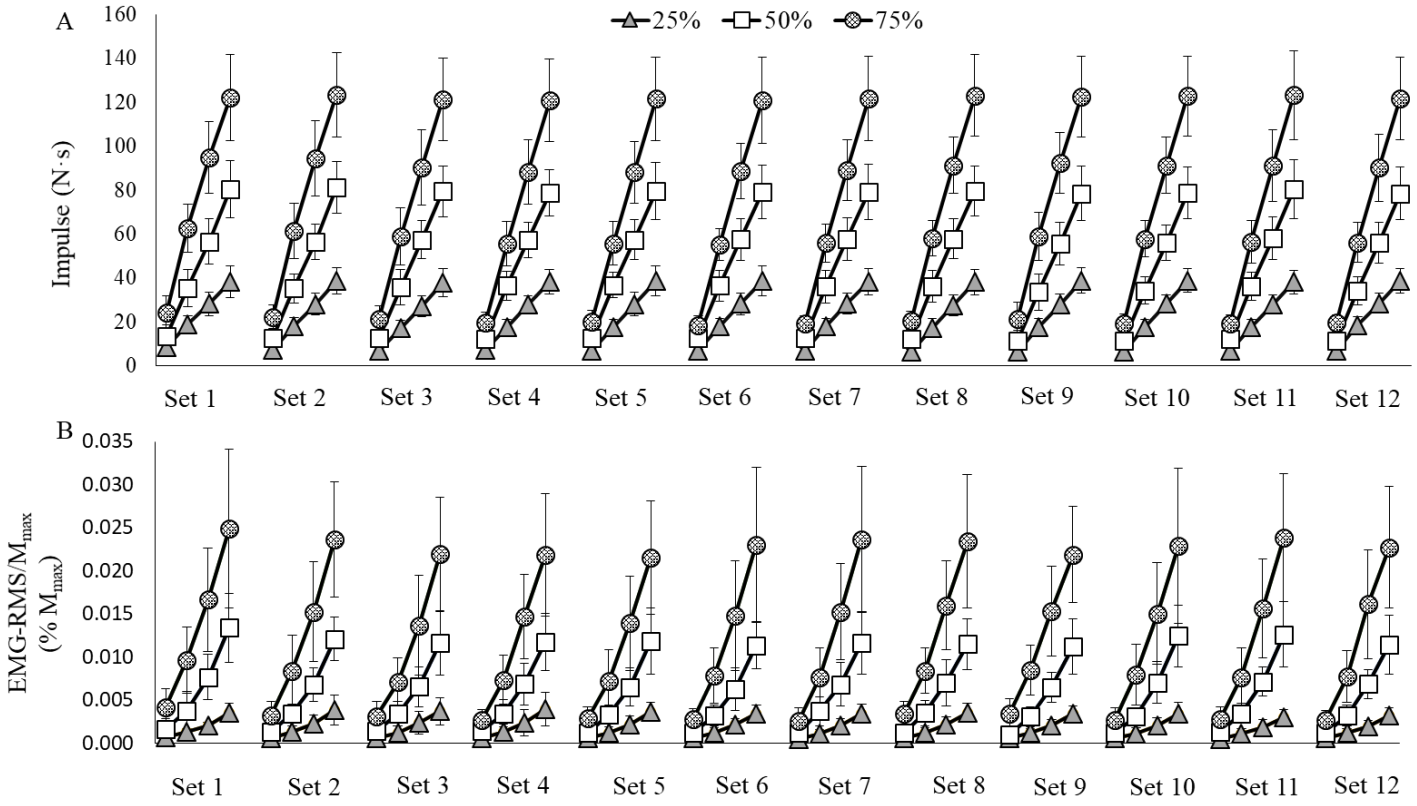

Figure 2. Force and muscle activity (EMG) during RT (n = 14 males). Impulse (A) and EMG_{RMS}/M_{max} (B) from the eight repetitions of each set (1^{st} – 12^{th}) during each training intervention (25%, 50% and 75% MVC) in the main experiment (mean ±SD). Results from each set are divided into four time intervals of 500ms.

5.4.1.1 MEP amplitudes and associated twitch forces

Figure 3 shows a representative individual example of MEPs and CMEPs obtained at rest after control, and acute RT at 25, 50 and 75% of MVC. MEP amplitudes increased more after RT at 75% compared to all the other sessions. Figure 4 shows that there were TIME ($F (7, 91) = 10.14$, $P < 0.001$; $\eta_p^2 = 0.44$), INTENSITY ($F (3, 39) = 20.17$, $P < 0.001$; $\eta_p^2 = 0.61$) and TIME x INTENSITY interaction effects ($F (21, 273) = 3.55$, $P < 0.001$; $\eta_p^2 = 0.21$). Overall, MEPs consistently increased over the 30 minutes after RT compared to baseline only after 75% session. The 50% session increased MEPs from 0' to 15' but the 25% and control sessions did not affect MEP size. The 75% session compared with other sessions produced the largest increases in MEP size during the last 15' (Fig. 4). Also, the INTENSITY main effect revealed greater sustained increases in MEPs after RT at 75% (+69.6%) compared with control (-5.3%, $P = 0.001$), 25 (+10.6%, $P = 0.001$), and 50% (+39.2%, $P = 0.026$) of MVC and also after RT at 50% vs control ($P = 0.008$) and 25% ($P = 0.024$) MVC (Fig. 4B).

MEP twitch forces increased more after RT at 75% than after the other sessions. There were TIME ($F (2.84, 36.98) = 23.83$, $P < 0.001$; $\eta_p^2 = 0.65$), INTENSITY ($F (1.49, 19.42) = 28.66$, $P < 0.001$; $\eta_p^2 = 0.69$) and TIME x INTENSITY interaction effects ($F (21, 273) = 5.44$, $P < 0.001$; $\eta_p^2 = 0.29$). As with MEPs, MEPs twitch forces consistently increased over the 30 minutes of measurements after RT with 75% MVC compared to baseline. The 50% session also increased MEP twitch forces compared to baseline but only immediately after training (0'). No changes occurred after the 25% and control sessions relative to baseline. Increases after RT with 75% were larger compared to the other sessions during the last 15 minutes (Fig.5). Furthermore the main effect of INTENSITY showed that the increases in MEP-associated twitch forces were the greatest after the 75% session (+83.1%; Control session: -9.8%; 25% session: +18.2%; 50% session: +38.5%, all $P < 0.001$, see Fig. 5B). The overall increases in MEP-associated twitch forces were also greater after RT at 25% and 50% compared with control session ($P = 0.016$ and $P = 0.009$, respectively; see Fig. 5B).

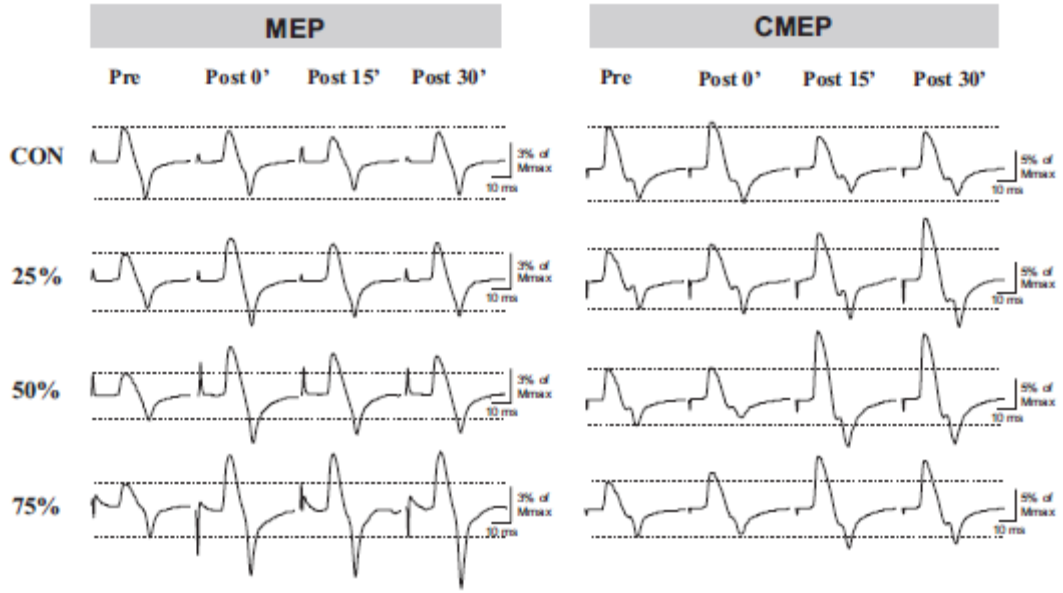

Figure 3. Raw traces of MEPs and CMEPs in one subject after control session and isometric RT at 25%, 50% and 75% of MVC. PRE motor evoked potentials represents the average of all the evoked potentials obtained at 15, 10 and five minutes before training. POST-0, POST-15 AND POST-30 represents the average of all evoked potentials obtained at each time point. Dashed line indicates the amplitude of PRE measurements.

5.4.1.2 CMEP amplitudes and associated twitch forces

CMEP amplitudes after acute RT were larger compared to the control session independently of the intensity. There were TIME ($F(2.66, 34.53) = 4.30$, $P = 0.014$; $\eta_p^2 = 0.25$) and INTENSITY ($F(3, 39) = 7.15$, $P = 0.001$; $\eta_p^2 = 0.34$) main effects but no TIME x INTENSITY interaction ($F(21, 252) = 1.24$, $P = 0.217$; $\eta_p^2 = 0.09$). Overall, there was an increase in CMEP amplitude after RT at any intensity (mean of +26.9%) compared to the control session (-14.9%, all $P < 0.05$ for all comparisons) but without differences between the other sessions (Fig. 4D). The increase after RT sessions was not different to baseline values at any point (Fig. 4C).

CMEP-associated twitch forces after acute RT were larger compared to the control session, independently of the intensity. There were TIME ($F(3.33, 43.36) =$

9.55, P < 0.001; η_p^2 = 0.42), INTENSITY (F (3, 39) = 7.75, P < 0.001; η_p^2 = 0.37) and a TIME x INTENSITY interaction (F (21, 273) = 3.53, P < 0.001; η_p^2 = 0.21) effects. CMEP-associated twitch forces increased compared to baseline values only from 0′ to 10′ after RT at 50% and 75% of MVC (Fig. 5C). The increase after 25%, 50%, and 75% sessions was only different compared to the control session during the first 20′ (Fig. 5C). Also, the main effect of INTENSITY showed that CMEP-associated twitch forces after 25%, 50% and 75% sessions (mean of +31.3%) was larger than the increase after the control session (-5%, all P < 0.05 for all comparisons) but without statistical differences between training at 25%, 50%, and 75% of MVC (Fig. 5D).

5.4.1.3 Maximal M-wave amplitudes and associated twitch forces

M_{max} amplitude did not change after any intervention (Fig. 4E, 4F). M_{max}-associated twitch forces increased immediately after acute RT and then returned to baseline values. There were TIME (F (2.25, 29.29) = 58.35, P < 0.001; η_p^2 = 0.82) INTENSITY (F (3, 39) = 5.31, P = 0.004; η_p^2 = 0.29) and TIME x INTENSITY interaction (F (21, 273) = 15.67, P < 0.001; η_p^2 = 0.55) effects. M_{max} twitch forces increased compared to baseline immediately after 25%, 50% and 75% sessions (0′ after RT, P = 0.003, P < 0.001, and P = 0.001, respectively). The increase in the M_{max}-associated twitch forces immediately after training (from 0′ after RT) was larger after the 50% and the 75% session compared to the control and 25% sessions. The INTENSITY main effect showed that M_{max} twitch forces did not differ between sessions (P > 0.05, see Fig. 5F).

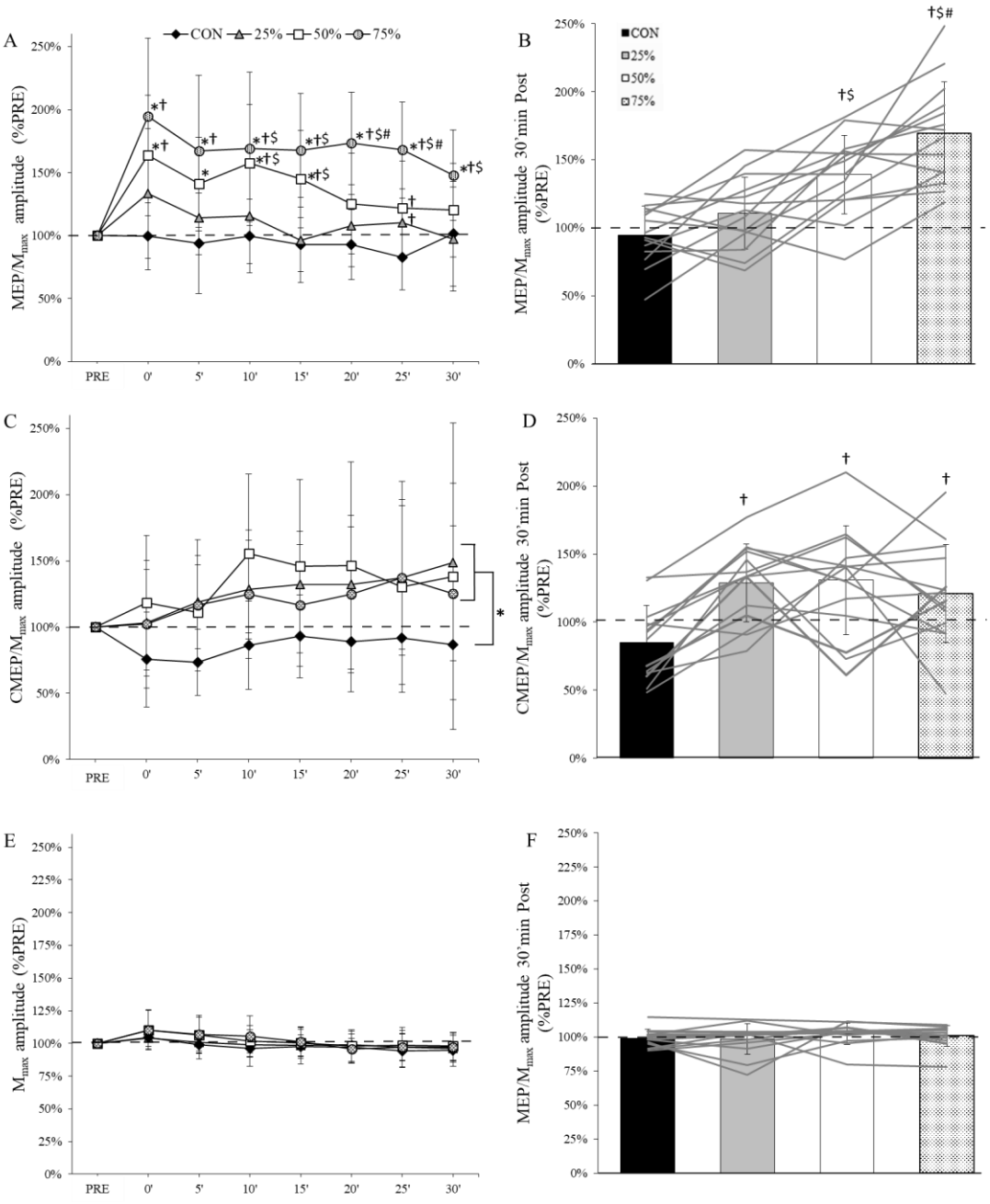

Figure 4. Time course of MEPs, CMEPs and M_{max} after RT (n = 14 males). Left panel shows the time course (mean ±SD) of the MEP/M_{max} (A), CMEP/ M_{max} (C), and M_{max} (E) of the right BB during the different RT sessions performed at 25%, 50%, and 75% of the MVC and during the CON

condition (Two-way RM-ANOVA with TIME and INTENSITY as factors). Each evoked potential was normalized to PRE values. Right panel shows the INTENSITY main effect for the MEP/M_{max} (B), CMEP/ M_{max} (D), and M_{max} (F) of right BB. (*) shows a statistically significant difference ($P < 0.05$) to PRE values; (†) means statistically significant ($P < 0.05$) with respect to CON ($P < 0.05$); ($) shows statistically significant difference ($P < 0.05$) with respect to 25%; (#) means statistically significant difference with respect to 50%.

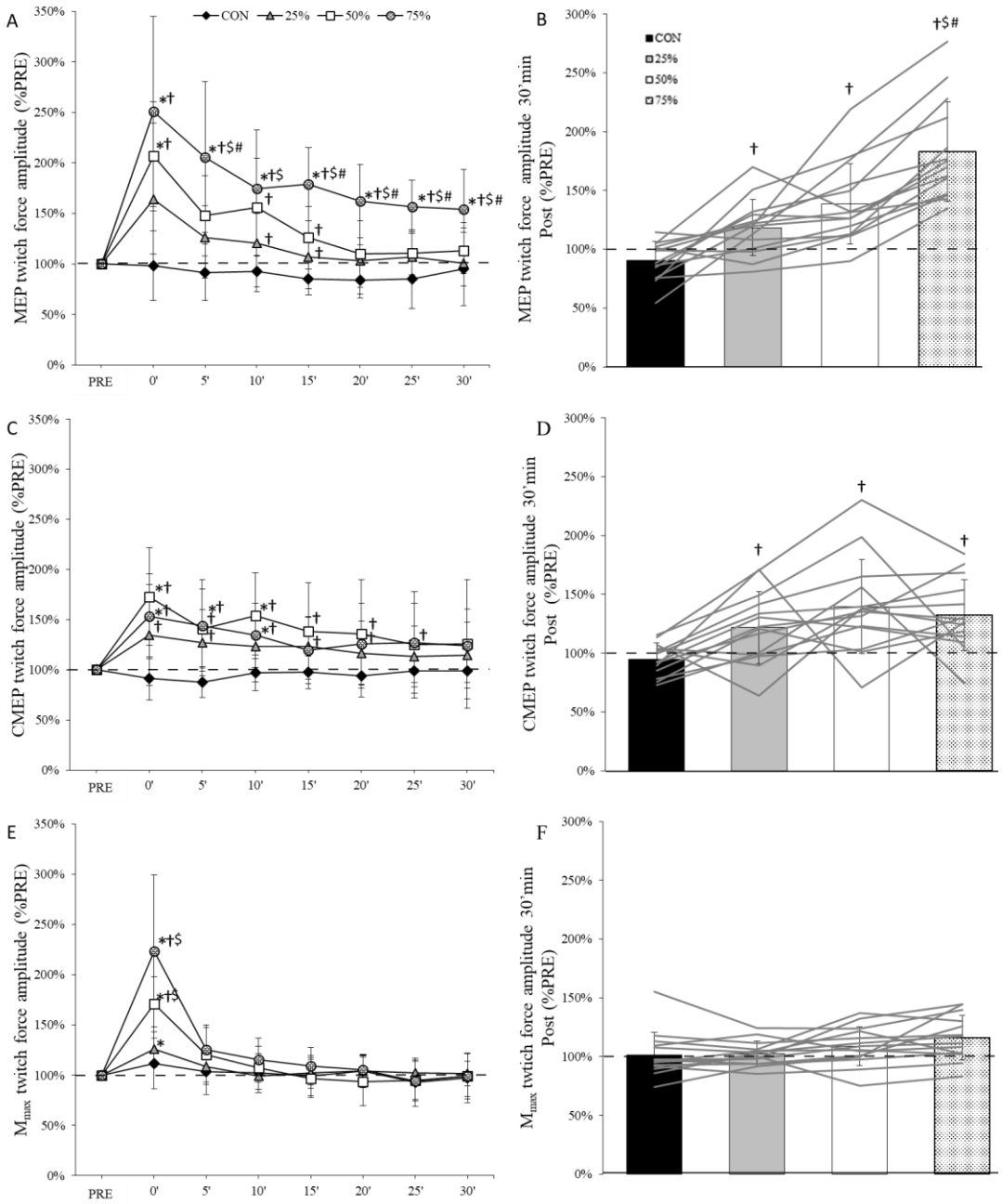

Figure 5. Time course of MEPs, CMEPs and M_{max} twitch forces after RT (n = 14 males). Left panel shows the time course (mean ±SD) of the associated twitches of MEP (A), CMEP (C), and M_{max} (E) of the right BB during the different RT sessions performed at 25%, 50%, and 75% of the MVC and during the CON condition (Two-way RM-ANOVA with TIME and INTENSITY as factors). Each

twitch was normalized to the PRE values. Right panel shows the INTENSITY main effect for the associated twitches of the MEP/M_{max} (B), CMEP/ M_{max} (D), and M_{max} (F) of the right BB. (*) shows a statistically significant difference ($P < 0.05$) to PRE values; (†) means statistically significant ($P < 0.05$) with respect to CON ($P < 0.05$); ($) shows statistically significant difference ($P < 0.05$) with respect to 25%; (#) means statistically significant difference with respect to 50%.

5.4.2 Complementary experiment

5.4.2.1 MEP amplitudes and associated twitch forces

Doubling the volume of RT at 25% of MVC produced larger MEP amplitudes. There were TIME ($F (7, 49) = 6.97$, $P < 0.001$; $\eta_p^2 = 0.50$) and VOLUME effects ($F (1, 7) = 11.53$, $P = 0.012$; $\eta_p^2 = 0.62$) but not a TIME x VOLUME interaction ($F (2.90, 20.29) = 2.10$, $P = 0.61$; $\eta_p^2 = 0.23$). The increase in MEP amplitude was larger after performing 24 sets instead of 12 sets at 25% of MVC ($P = 0.012$, see Fig. 6A). However, pairwise comparisons for the main effect of time showed larger MEP amplitudes compared to baseline only at 0′ and 10′ after both training sessions ($P = 0.047$ and $P = 0.022$, respectively).

Performing 24 sets instead of 12 at 25% of MVC produced also larger increases in MEP-associated twitch forces ($P = 0.037$, see Fig. 6B). There were TIME ($F (2.35, 16.43) = 14.02$, $P < 0.001$; $\eta_p^2 = 0.67$), VOLUME ($F (1, 7) = 6.64$, $P = 0.037$; $\eta_p^2 = 0.49$) and TIME x VOLUME interaction ($F (7, 49) = 3.29$, $P = 0.006$; $\eta_p^2 = 0.32$) effects. However, pairwise comparisons showed that MEP-associated twitch forces were not significantly different compared to baseline after any training session. The increase in MEP-associated twitch forces was significantly larger after performing 24 sets compared to 12 sets at 25% only at 0′ after RT ($P = 0.035$).

5.4.2.2 CMEP amplitudes and associated twitch forces

CMEP amplitude and CMEP-associated twitch forces did not change after any intervention (Fig. 6C, 6D).

5.4.2.3 M_{max} amplitudes and associated twitch forces

For M_{max} obtained at rest, there was a VOLUME ($F (1, 7) = 5.96$, $P = 0.045$; $\eta_p^2 = 0.46$) main effect but not a TIME ($F (1.92, 13.42) = 1.56$, $P = 0.171$; $\eta_p^2 = 0.18$) or

TIME x VOLUME interaction (F (3.41, 23.85) = 2.51, P = 0.77; η_p^2 = 0.26) effect. Pairwise comparisons showed a statistically larger increase in M_{max} after performing 24 sets compared to 12 sets at 25% (P = 0.045, see Fig. 6E).

For M_{max}-associated twitch forces, there was a main effect of TIME (F (3.09, 21.62) = 12.93, P < 0.001; η_p^2 = 0.65) but not VOLUME (F (1, 7) = 1.52, P = 0.257; η_p^2 = 0.18) or TIME x VOLUME interaction (F (7, 49) = 0.84, P = 0.557; η_p^2 = 0.11) effect. Pairwise comparisons showed a statistically larger increase in M_{max} twitch forces compared to baseline only at 0' after RT independent of training volume (P = 0.031).

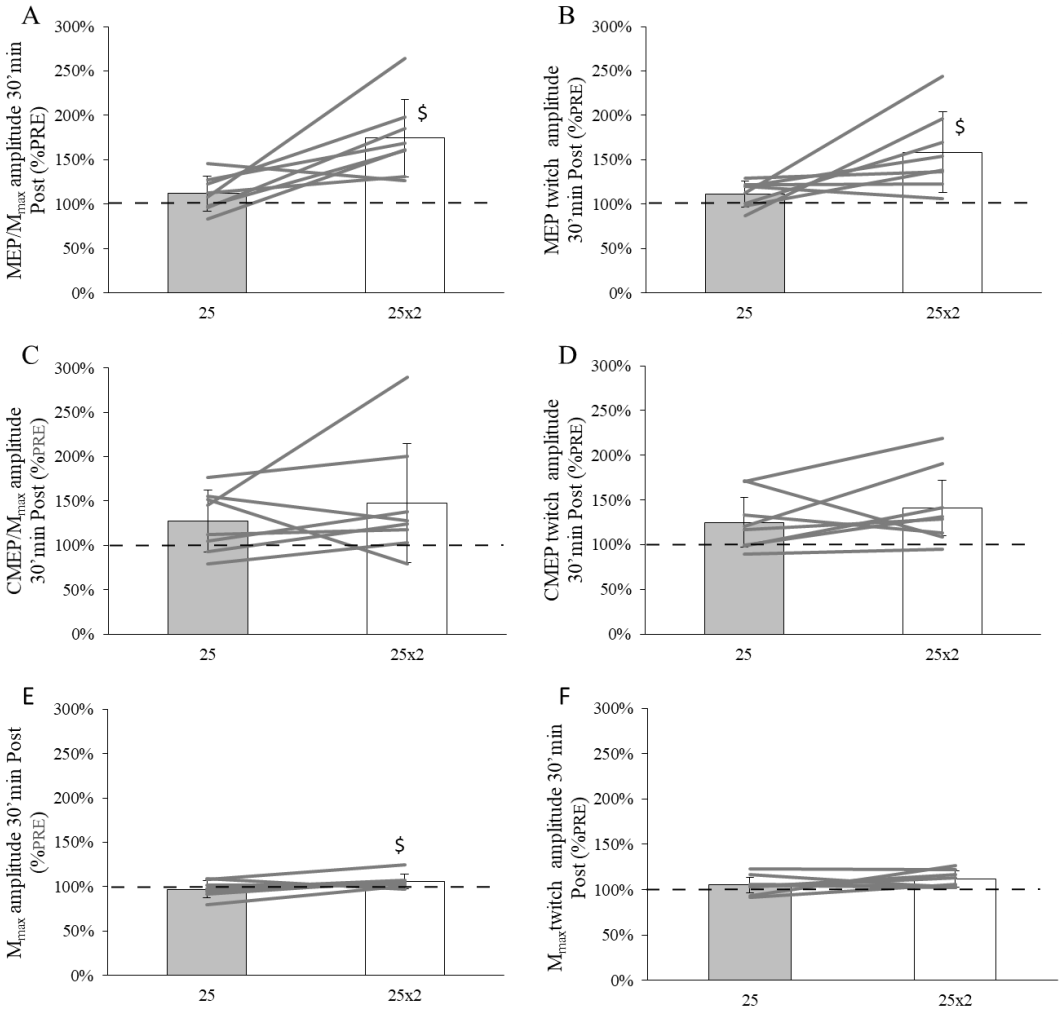

Figure 6. VOLUME main effect for MEPs, CMEPs and M_{max} and associated twitches after low intensity and double volume low intensity RT (n = 8 males, two-way RM-ANOVA). Left panel

shows the overall net change (i.e.: average of all measures obtained after each training session normalized to PRE values (mean ±SD)) for the MEP/M_{max} (A), CMEP/ M_{max} (C), and M_{max} (E) of right BB. Right panel shows the overall net change (i.e.: average of all measures obtained after each training session normalized to PRE values) for the associated twitches of the MEP/M_{max} (B), CMEP/ M_{max} (D), and M_{max} (F) of the right BB. ($) shows statistically significant difference ($P < 0.05$) with respect to 25%.

5.5 DISCUSSION

5.5.1 Main experiment

The data show for the first time that the intensity of acute isometric RT of the elbow flexors affects cortical excitability measured at rest in healthy men. In agreement with the hypothesis, MEP amplitude and the associated twitch forces increased with RT intensity but, contrary to the hypothesis, the changes in CMEP amplitude and twitch forces were independent of RT intensity. Also the duration of the effect on TMS responses increased with RT intensity. The data suggest that the intensity of muscle contraction used in acute bouts of RT affects cortical excitability.

Our results expand previous data by showing dose-response effects of RT intensity on CSE measured at rest. Acute bouts of RT can increase the responses to stimulation of the corticospinal tract at cortical (75-77, 260, 383) and spinal levels (77), suggesting an increase in cortical or α-motoneuron excitability or an increase in the efficacy of the corticospinal-motoneuronal synapse. Our results show that CMEPs and associated twitch forces increased after RT independent of training intensity in comparison to the control session. However, CMEPs were not different to baseline after RT (Fig. 4C), suggesting that spinal adaptations measured at rest after acute RT do not always occur (47).

Regarding responses to TMS, our data show that MEPs measured at rest increased by 95%, 64%, and 35% just a minute after the last contraction of an acute bout of isometric RT at 75%, 50%, and 25% of MVC and that the increase after RT at 75% was larger compared with the increases after RT at lower intensities. Considering the 75% condition, the 95% increase was smaller than the 242% increase reported previously (77), a difference that could be related to the position

of the shoulder being flexed to 90º and forearm supinated vs. shoulder abducted and forearm pronated (77). Such differences in joint positions could affect the responses to TMS and cervicomedullary stimulation (166, 167). Also in our study the rate of force development (RFD) systematically increased with contraction intensity and could confound the observed dose effects. However, RFD does not seem to be a determinant of corticospinal responses to acute RT (75, 77).

When normalized to M_{max}, the responses to M1 stimulation by TMS involve cortical and spinal mechanisms (176). However, α-motoneuron excitability and the efficacy of the corticospinal-motoneuronal synapse are the mechanisms involved in CMEPs normalized to M_{max}, which did not vary with RT intensity. Furthermore, contrary to MEPs, CMEPs did not increase immediately after RT. It thus seems that the intensity-dependent TMS responses to RT reflect cortical involvement. Indeed, Dai et al. (73) showed that higher forces led to correlated increases in activation of motor cortical neurons and interneurons to generate the desired motor output. Furthermore, there is additional evidence for a lack of adaptation at the spinal level after short duration high-intensity RT as measured by cervicomedullary stimulation (47) and H-reflex (43). Thus, the emerging picture is that initial neural adaptations to RT are localized at a supraspinal level (43). The increases in MEP size after RT are probably a reflection of changes in excitatory-inhibitory balance toward greater efficacy of the excitatory input to the trained muscles. One way this can happen is that cortical excitability increases while the efficacy of GABAergic inhibitory interneurons decreases, or both (76, 78, 265).

The MEP- and CMEP-associated twitch forces also increased after RT, but training intensity affected only the increases in MEP twitch forces. Twitch forces evoked by non-focal stimulation like TMS or corticospinal tract electrical stimulation reflect the sum of the forces of different muscles around the joint, including the antagonist elbow extensors (77). Therefore, although not intensity-dependent, the increase in the twitch force elicited by cervicomedullary electrical stimulation during the first 10 minutes reflects some increase in α-motoneuron excitability or the efficacy of the corticospinal-motoneuronal synapse (77) occurring preferentially in the α-motoneurons projecting to the elbow flexors. Also, the intensity-dependent increase in the twitch forces evoked by TMS reflects that the intensity of training influenced the increase in the output of the cortical

neurons projecting mainly to the elbow flexors. Some potentiation at the peripheral level also occurred because the M_{max}-associated twitch forces increased immediately after the protocol. This potentiation could have influenced the increase in MEP- and CMEP-associated twitch forces after RT during the first 10 minutes but probably did not influence the rest of measurements (77).

Our results show that not only did RT intensity affect the magnitude of increases in cortical excitability, it also affected its duration. This longer lasting effect is probably related to the larger increase produced by the higher intensities immediately after RT ended. However, as was the case for magnitude, the duration of the effect of RT in CMEPs was independent of exercise intensity. The dose-dependent lasting rise in cortical excitability could be related to use-dependent corticomotor plasticity mediated by LTP-like mechanisms (385, 386), which can be present up to an hour after motor practice is stopped (244, 385-388). However, previous studies questioned the role of plastic changes in the corticospinal pathway measured by TMS in the neural adaptations to simple RT tasks (31). Therefore, it is possible that the characteristics of the task, generating progressively higher force in response to the visual cue, and not RT per-se, could underlie the acute corticospinal responses we observed. Indeed, CSE increases and cortical inhibition decreases after skill training and metronome paced RT but not self-paced RT (31, 76). This suggests that synchronization to a visual or audible cue could be more important to modulate the neural mechanisms than contraction intensity per se. However, our results show that in a task in which participants increase force by tracking a visual template, cortical responses to TMS scale with contraction intensity, leading to an effort-dependent sensitization of cortico-cortical cells in M1 that strengthens the intracortical neuronal ensembles generating outputs towards the trained muscles (385).

The increase in the net excitatory output from M1 measured by single pulse stimuli could be related to a compensatory mechanism to counteract peripheral fatigue (260). However, although we cannot discard the presence of some peripheral fatigue, it was probably low, since there were no significant decreases in M_{max} associated twitch forces during the 30 minutes after the interventions. Furthermore, the EMG_{RMS} amplitude during the training sets remained constant, suggesting that a compensatory increase in central drive was not needed to counteract reductions in muscle contractile properties or α-motoneuron

excitability. Regarding central fatigue, although our data cannot discard the possibility of increased cortical inhibition, MEPs tended to remain depressed for over 10 minutes when recorded at rest after fatiguing contractions (393). This depression contrasts with the increase in MEPs size and associated twitch forces for 25-30 minutes after RT ended (Fig. 4A and 5A). Also, if fatigue had affected α-motoneuron excitability, it would have reduced the responses to cervicomedullary electrical stimulation at rest (393), which is also in contrast with our findings. As a limitation to our study we did not measure MVC after RT and, therefore, we cannot unequivocally rule out the effects of fatigue on the outcome measures.

Nonetheless, the acute changes in corticospinal response to a single bout of RT likely reflect initial neural adaptations to RT (75, 77) rather than a compensation for fatigue. Thus, our finding of a contraction intensity-dependent effect on cortical excitability could explain the absence of chronic neural adaptations (59, 97) (i.e., no changes in EMG, V-wave, voluntary activation) and the smaller MVC force increases that occur with low- compared to high intensity RT (96).

5.5.2 Complementary experiment

High compared with low exercise volume tends to produce greater increases in performance (394) and muscle mass (292). We found that a doubling of exercise volume increased MEP and associated twitch forces compared with the responses after the 25% intensity protocol without differences in CMEP size and associated twitch forces. Our data agree with a study reporting that training duration affected the involuntary twitch responses generated by TMS toward the training direction after ballistic training (245). These results suggest that the volume of an acute isometric RT session of the elbow flexors also affected cortical excitability at rest in healthy men. However, we must be cautious with this conclusion because samples size was small in our complementary experiment.

5.6 LIMITATIONS

We did not match the size of MEPs and CMEPs, invalidating any comparisons between the two responses. However, as has been also argued (77), the time course of changes in MEP and CMEPs was different, with marked increases in MEP amplitude immediately after training in contrast to no changes in CMEPs at 10 minutes post-training. Also, the larger baseline size of CMEPs (10% of M_{max}) could have reduced the potential for change. However, this is unlikely because CMEPs of larger baseline size (15-20% of M_{max}) increased to a greater extent after high intensity RT (27) compared with the changes we observed. Future studies should match the size of MEPs and CMEPs, an approach that would make it possible to determine more accurately if the site of neural adaptation to RT is at the spinal or cortical level.

5.7 CONCLUSION

Collectively our data tentatively suggest that the intensity of muscle contraction used in acute bouts of RT affects cortical excitability. The dose effects are probably related to the heightened cortical activation, resulting in greater adaptive processes in M1. Additionally, volume of acute RT also seems to contribute to the acute changes in cortical excitability. Future studies will determine if there is a dose-response relationship between MVC force and neuronal excitability after chronic RT.

VI – STUDY 2

VI – STUDY 2

Effects of acute and chronic resistance training variables on ipsilateral motor cortical excitability and cross-education: A systematic review

6.1 ABSTRACT

Objective: The increase in voluntary force of an untrained limb (i.e. CE) after unilateral RT is believed to be a consequence of cortical adaptations. However, studies measuring neurophysiological adaptations with TMS found inconsistent results. One unexamined factor contributing to the conflicting data is the variation in the type and intensity of muscle contractions, fatigue, and the strategies of pacing the movement. Therefore, the purpose was to analyze how those unilateral RT variables affect the adaptations in ipsilateral M1 and CE. Methods: We performed a systematic literature review, using the databases MEDLINE (via PubMed) and Web of Science with the search terms with Boolean conjunctions: "Transcranial magnetic stimulation" AND "Ipsilateral cortex" AND "Resistance training". Results. The 11 acute and 12 chronic studies included partially support the idea of increased cortical excitability and reduced intracortical inhibition in the ipsilateral M1, but the inconsistency between studies was high. Conclusions: Differences in type and intensity of contraction, fatigue, and strategies of pacing the movement contributed to the inconsistencies. The tentative conclusion is that high intensity eccentric or externally-paced contractions are effective to increase the ipsilateral M1 excitability but CE can occur in the absence of such changes. Thus, the mechanism of the CE examined with TMS remains unclear.

6.2 INTRODUCTION

Unilateral muscle contractions activate contralateral but also ipsilateral brain structures (73). Such ipsilateral brain activation occurs during the execution of simple motor skills requiring little effort and parametrically increases with the intensity of isometric and dynamic muscle contraction (115, 181, 199). However, the source of this ipsilateral brain activation is not entirely clear. Because the delay between the activation in the two hemispheres is in the millisecond range, a part of the activation is likely to occur simultaneously and inadvertently, while there is a temporal element of this activation that is due to interhemispheric actions acting on intracortical circuits in the ipsilateral hemisphere (203).

Short-term unilateral RT produces not only increases in voluntary muscle force of the trained muscle but also in the non-practice homologous muscle, a phenomenon known as CE (19). Although short-term motor skill training also leads to interlimb transfer of skill (395, 396), the present review focuses only on the CE of voluntary muscle force. Typically, CE is muscle-specific but without (or little) peripheral adaptations in the untrained muscle itself (321). By default, CE after unilateral RT was assumed to have a neural origin (67). At least two neural mechanisms can (partly) explain CE after unilateral RT. One is related to the possibility that the repeated activation of the ipsilateral brain structures by the unilateral muscle contractions during unilateral RT serves as the training stimulus for adaptations in the ipsilateral brain areas. Such a mechanism is supported by the increase in the number of corticospinal neurons recruited in the untrained limb (109, 325, 337) and reductions in intracortical inhibition (39, 89, 327, 336). In other words, cross-activation during unilateral contractions leads to neuroplastic changes in both cortices (66, 67) that increase the output produced by the motor command, potentially explaining behavioural gains in the untrained limb. A second potential mechanism is an altered interhemispheric communication after unilateral RT (325) that can also influence SICI and long intracortical inhibition circuits in the transfer hemisphere (115) and, thus, be the basis for CE.

However, despite the solid theoretical foundation for this hypothesis, there are many inconsistencies in the effects of acute or chronic unilateral RT on ipsilateral M1 excitability quantified by ipsilateral CSE, ipsilateral intracortical

inhibition, and ipsilateral facilitation, making it difficult to determine the neural mechanisms underlying CE. It is possible that the inconsistencies are due to the differences between studies with respect to training variables such as the intensity (199) and the type of muscle contraction (112), the degree of fatigue, and the external pacing of muscle contraction (76), which can affect the adaptations in the ipsilateral M1. Thus, it is probably that those training variables per se affect the acute and chronic adaptations in the ipsilateral M1 excitability, and hence CE.

Therefore, the purpose of this review is to determine the effects of the type of muscle contraction, the training intensity, the degree of fatigue and the external pacing of muscle contractions on the ipsilateral M1 adaptations. Also to determine if ipsilateral M1 adaptations are related to the effectiveness of the motor command, producing correlated increases in CE following acute and chronic unilateral RT in healthy adults.

6.3 METHODS

The present systematic review was performed according to the 'Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols' (PRISMA-P) 2015 guidelines (397).

6.3.1 Search strategy

A systematic literature review included papers published between January 1950 and March 2018 in the online databases MEDLINE (via PubMed) and Web of Science. The main search terms were "Transcranial magnetic stimulation", AND "Ipsilateral cortex", AND "Resistance training", and its synonyms. Tracking of cited studies and hand searching of relevant articles were also completed. The literature search was conducted by DCP. The authors were contacted to provide the data missing from original papers but needed for the review.

6.3.2 Eligibility criteria and study selection

After removal of duplicates, the remaining studies were screened manually based on title, abstract, and full-text. To guide the exclusion and inclusion criteria we followed the PICOS guidelines (Population, Intervention, Comparator,

Outcomes, and Study) (398).The following PICOS criteria were applied. (i) Population: healthy adults (free of orthopaedic and neurological conditions) age 18 to 55 years. (ii) Intervention: Unilateral RT session was considered as a unilateral repetitive task at a given percent of 1RM, absolute load (Kg), if the task was dynamic, or percent MVC, if the task was isometric, while the other limb was at rest. Duration of unilateral RT was defined as a minimum of two sessions per week for at least two weeks for the chronic studies. (iii) Comparator: For chronic studies, a control group that did receive no intervention or a no-intervention control period for the experimental group served as comparators. For acute studies, not control intervention was required. (iv) Outcomes: Adaptations in the ipsilateral M1 had to be measured with TMS using different stimulation protocols. At least one of the following outcome parameters measured in the ipsilateral M1 was necessary for inclusion of the respective study: MEP amplitude, SICI, IHI, ICF or contralateral SP before and after unilateral RT. (v) Study: randomized trial were included.

Studies were excluded that used sustained unilateral muscle contractions to fatigue or to a time limit, used electrical muscle stimulation, or direct/placebo stimulation of the corticospinal tract (EMS, a-tDCS, PAS, rTMS...). A consensus among three of the authors (DCP, GM, and TH) guaranteed that the studies included in the review met the inclusion.

6.3.3 Coding

We coded the data for authors, publication date, sample size, participants' characteristics (age, limb dominance), muscle group trained, details of RT intervention (duration, sessions, volume, intensity, exercise type), key outcome (TMS measurements and strength measures for case of chronic studies), and results of the study regarding the key outcomes.

6.3.4 Assessment of methodological quality

We computed the PEDro score to assess the methodological quality of the included studies (399). The scale consists of 11 criteria, of which the first is not included in the total score. Each criterion is rated "yes" or "no," and a "yes"

should only be awarded when a criterion is clearly satisfied. If all criteria are satisfied, the maximum score of 10 can be given. Included studies with a PEDro score of ≥ 6/10 were considered of high quality, whereas a score of 5/10 or lower was considered as low methodological quality. Two researchers (DCP, SRA) independently assessed the methodological quality and discrepancies were resolved by discussion until consensus was reached. Additionally we also assessed the methodological quality of the acute studies without control group using the 'Quality assessment tool for before-after studies with no control group' (400), a 12-question tool which rates the methodological quality of the studies as "good", "fair" or "poor" (7 studies). The raters were not blinded to study authors, place of publication, and results.

6.4 RESULTS

6.4.1 Search results

Figure 7 shows the flow diagram of the systematic review. The search identified 687 studies. After duplicates, 518 studies were left. After checking the titles, abstracts, and the full-text as needed, 22 studies met the inclusion criteria, 11 to analyse the acute effects, and 12 studies to analyse for chronic effects (one study was included in both analysis).

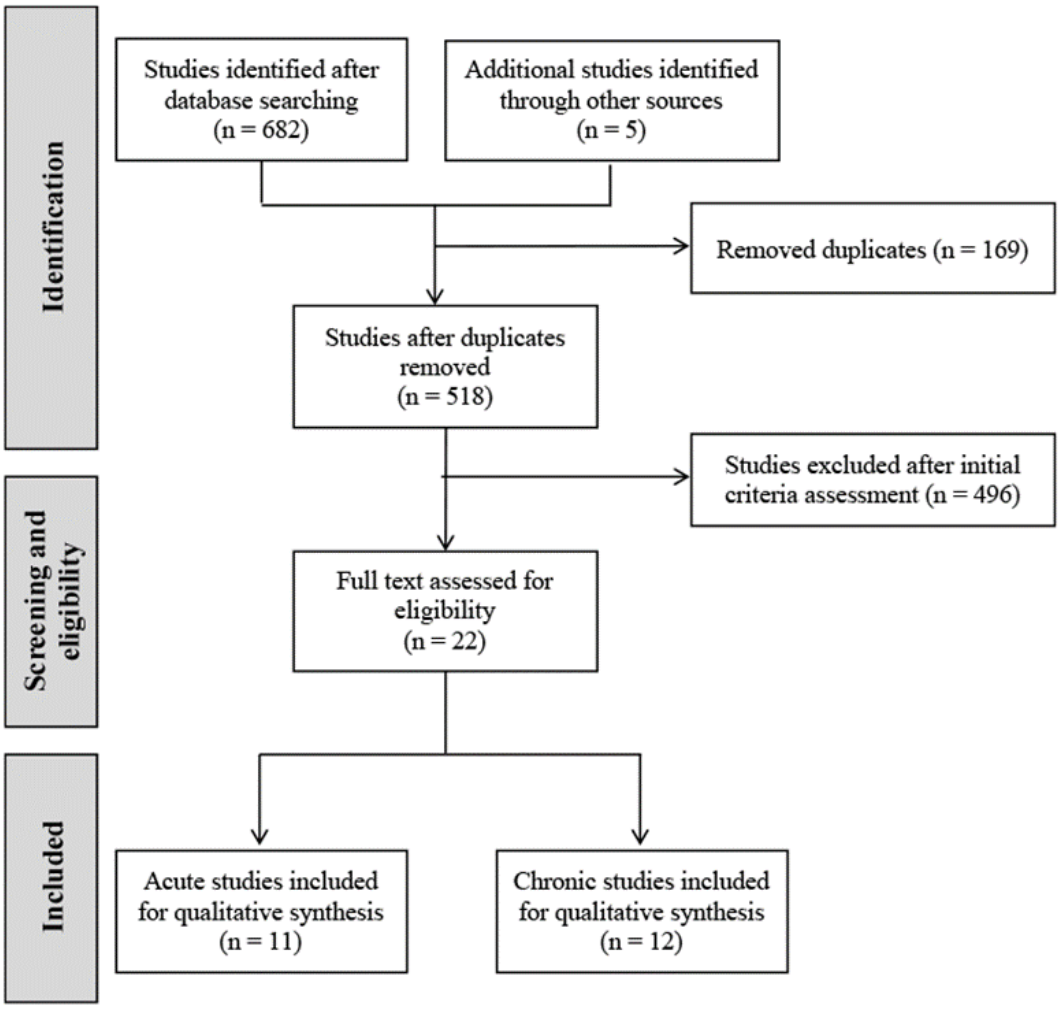

Figure 7. Flow diagram of studies identified, excluded, and included in the systematic review.

6.4.2 Quality assessment

Tables 2 and 3 show the quality scores. 75% of the studies revealed a high quality PEDro score (≥6 points). The methodological quality of the before-after studies without a control group was "fair".

6.4.3 Participants and study characteristics

6.4.3.1 Acute studies.

Table 2 summarize the study characteristics using dynamic and isometric muscle contraction as a training stimulus. The 11 studies were published between 2002 and 2015. The sample size per study ranged between eight and 32 (mean 15.4, total N = 174), and participants' age was 19 to 55 years. Two of the 11 studies reported subjects' training status, with one including a mix of sedentary, endurance, and resistance-trained participants (401), and the other including subjects with no experience in strength training of the fingers (325). Most participants were right handed, whereas in four studies there were both, right and left handed subjects (total of 11 left handed subjects) (76, 401-403).

All but one study (404) trained an upper extremity muscle. Participants trained the dominant (n = 7 studies) (325, 401-406) or the non-dominant limb (n = 4 studies) (76, 407-409). Studies included dynamic (76, 401, 405, 408) and static (325, 402-404, 406, 407, 409) muscle contractions. Five studies included at least one situation in which the specified training was performed until they could no longer complete the movement (401, 405, 408), achieve the desired force level (409) or even until they could no longer exert any force (complete exhaustion) (407). In eight studies, there was at least one intervention without an explicit intention to perform contractions until complete exhaustion (76, 325, 402-404, 406). Regarding training intensity, six studies used low intensity contractions (1%-30% of 1RM or MVC) (401, 404-406, 408, 409), four studies used medium intensity (31-60% of 1RM or MVC) (402, 403, 407, 409), and two studies used high intensity contractions (> 61% of 1RM or MVC) (76, 325).

Table 2. Acute effects of one session of dynamic (n = 4) and static (n = 7) RT on ipsilateral TMS measurements

Study	Sample	Muscle group	Intervention	Neurophysiological measures	Main outcomes	Quality
Bäumer et al. (2002)	n = 10 (all RHD) Age range: 27–38 yrs Gender: All ♂	Right FDI	Experiment 1: Left hand repetitive pinch grips (1–2 Hz) of 50% of MVC, until the inability to reach the required force level.	CSE, SICI, and ICF at rest	CSE and SICI: ↔ ICF: ↓* 96% after 2-6 min. ↔ after 15-19 min	Fair
			Experiment 2: Same intervention (same volume) without fatigue with 5% MVC contractions.	CSE, SICI, and ICF at rest	CSE, SICI, and ICF: ↔	
Edgley and Winter (2004)	n = 9 (all RHD) Age range: 21-42 yrs Gender: 4♀; 5♂	Right FDI	Left pinch grips against spring-loaded levers separated by 10 cm until subjects were unable to close levers.	CSE and IHI during contraction	CSE and IHI: ↔	Fair
Gorsler et al. (2004)	n = 20 (all RHD) Age range: 20–39 yrs Gender: All ♂	Left FDI	30 min of right handed pinch grips of 2% of MVC every 3 s	CSE and 6ms ISI paired pulse stimulation during contraction	CSE: ↔ Facilitation of paired pulse stimulation (6ms ISI) during trained limb contraction was ↓*	Fair
Humphry et al. (2004)	n = 8 (all RHD) Age range: 19-25 yrs Gender: 1♀; 6♂	Left BB	Elbow flexions against 3.5 kg at a frequency of 1Hz.	Experiment 1: Until exhaustion CSE at rest	↓* 60.6 ± 4.9% after 10-18minutes. ↔ after 40 minutes	Fair
			Experiment 2: Until 25% of time to exhaustion CSE at rest		↔ Just after. ↑* 166.5 ± 4.6% after 10 minutes to 60 minutes.	
Triscott et al. (2008)	n = 24 (19 RHD, 5 LHD) Age range: 20-57 yrs Gender: 3♀; 21♂	Dominant BB	Non-dominant elbow flexions against 4.5 kg until exhaustion	Sedentary subjects (n =8) CSE at rest	↓* 38-27% during the first 20 minutes	Fair
				Resistance trained subjects (n =8) CSE at rest	↓* 53-26% during the first 30 minutes	
				Endurance trained subjects (n =8) CSE at rest	↓* 47-38% during the first 10 minutes	
Takahashi et al. (2009)	n = 17 (all RHD) Age range: 21–24 yrs Gender: All ♂	Right FDI	Repeated left hand grips of 50% (1Hz) of MVC until complete exhaustion	CSE, SICI, and ICF at rest.	CSE: ↔ immediately after, ↓* 15% from 5 to 15 minutes after. SICI: ↓* 57% from 5 to 15 minutes after. ICF: ↔	Fair

Table 2. Acute effects of one session of dynamic (n = 4) and static (n = 7) RT on ipsilateral TMS measurements

Study	Sample	Muscle group	Intervention	Neurophysiological measures	Main outcomes	Quality
Hortobagyi et al. (2011)	n = 20 (all RHD) Age range: 30.9 ± 1.4 yrs Gender: 8♀; 12♂	Right FDI	Intervention group (n = 12): 5 sets × 10 reps at 80% of MVC of isometric index finger abduction. Tempo: 5" contraction – 5" rest	CSE, SICI, IHI, and ICF at rest.	CSE, SICI, and ICF: ↔ IHI: ↓* 8.9%	**6**
			Control group (n = 8): Without training	CSE, SICI, IHI, and ICF at rest.	CSE, SICI, and ICF: ↔ IHI: ↓* 1.8%	
Schmidt et al. (2011)	n = 11 (9 RHD, 2 LHD) Age: 27.3 ± 7.8 yrs Gender: 4♀; 7♂	Left FDI	10 sets × 50 reps of isometric right thumb abductions of an intensity of 35% of MVC paced with a temporal target (0.5Hz)	CSE, SICI, and ICF at rest.	CSE and SICI: ↔ ICF: ↓* 27.3% immediately after training	Fair
Lagerquist et al. (2012)	n = 10 (all RHD) Age range: 22-44 yrs Gender: 3♀; 7♂	Left Soleus	Voluntary isometric contractions at 20% of MVC (5" contraction – 5" rest) for 40 min	CSE during contraction	CSE: ↔	6
			Control condition with no training	CSE during contraction	CSE: ↔	
Goodall et al. (2013)	n = 13 (12 RHD, 1 LHD) Age: 40 ± 12 yrs Gender: 3♀; 10♂	Non-dominant FPB	15 min of intermittent isometric pinch task at 35% of MVC (5" contraction – 5" rest).	CSE at rest	CSE: ↔	6
			Control condition with no training	CSE at rest	CSE: ↔	
Leung et al. (2015)	n = 32 (29 RHD, 3 LHD) Age: 26.1 ± 6.8 yrs Gender: 20♀; 24♂	Non-dominant BB	Metronome paced (n = 11): Dominant elbow flexion: 4 sets × 6-8 reps at 70-80% of 1-RM. Tempo: 3 s concentric – 4 s eccentric	CSE and SICI during contraction	CSE: ↑* 43.3 ± 4.9% SICI: ↓* 20.3 ± 4.6%	6
			Self-paced (n = 11): Dominant elbow flexion: 4 sets × 6-8 reps at 70-80% of 1-RM. Tempo: Preferred tempo	CSE and SICI during contraction	CSE and SICI: ↔	
			Control group (n = 10): Without training	CSE and SICI during contraction	CSE and SICI: ↔	

6.4.3.2 Chronic studies.

Table 3 summarize chronic studies, published between 2011 and 2018 using dynamic or isometric contractions during training. The studies used a pre-post design, with all but one study including a no-intervention control group or control period (89). The sample size ranged from four (410) to 34 (332) subjects (mean 21.08 ± 8.2, n = 253). Participants were untrained (74, 90, 109, 325, 327, 336, 337, 410) or training status was not reported. 248 of 253 subjects were right-handed with an age of 18 to 35 years (but see (410)).

Nine chronic studies trained an upper extremity muscle (74, 89, 109, 325, 327, 332, 336, 337, 410) and three targeted a leg muscle (39, 90, 335). Training duration lasted for three to eight weeks with nine to 24 sessions. All but two studies (325, 332) used dynamic contractions. All studies used an intensity of 70% to 100% of 1RM, with a median of 80% of 1RM.

Table 3. Chronic effects of dynamic (n = 10) and static (n = 2) RT on ipsilateral TMS measurements and untrained limb strength.

Study	Sample	Muscle group	Intervention	Neurophysiological measures	Main outcomes	Δ strength of untrained limb	Quality
Hortobagyi et al. (2011)	n = 20 (all RHD) Age: 30.9 ± 1.4 yrs Gender: 8♀; 12♂	Right FDI	Intervention group (n= 12): 8 weeks, 20 sessions of 5 sets × 10 reps at 80% of MVC of isometric index finger abduction. Tempo: 5" contraction – 5" rest	CSE, SICI, IHI, and ICF at rest, and during trained limb contraction	CSE: ↑* 6% at rest and ↑* 10%, or 64% during trained limb contraction of 20 or 80% of MVC, respectively. SICI: ↔ ICF: ↔ IHI: ↓* 31%	↑* 21.8±2.3%	6
			Control group (n = 8): Without training	CSE, SICI, IHI, and ICF at rest, and during trained limb contraction	CSE: ↔ SICI: ↔ ICF: ↔ IHI: ↔	↔	
Kidgell et al. (2011)	n = 23 (all RHD) Age: 22.4 yrs Gender: 10♀; 13♂	Right BB	Intervention group (n = 13): 4 weeks, 12 sessions of 4 sets × 6-8 reps at 80% of 1-RM of unilateral dynamic elbow flexion. Tempo: 3" concentric – 4" eccentric	CSE and SP during contraction	CSE: ↑* 33% SP: ↔	↑* 19.2% (11.3 ± 4.9 Kg to 13.7 ± 5.4 Kg)	6
			Control group (n = 10): Control period without training	CSE and SP during contraction	CSE and SP: ↔	↔	
Goodwill et al. (2012a)	n = 14 (all RLD) Age: 21 ± 1.1 yrs Gender: 7♀; 7♂	Right RF	Intervention group (n = 7): 3 weeks, 9 sessions of 4 sets × 6-8 reps at 75% - 80% of 1-RM of single leg squats. Tempo: 3" concentric – 4" eccentric	CSE during contraction and SICI at rest	CSE: ↑* 32% SICI: ↓* 24.56%	↑* 35.4%	6
			Control group (n = 7): Control period without training	CSE during contraction and SICI at rest	CSE and SICI: ↔	↔	
Goodwill et al. (2012b)	n = 14 (all RLD) Age: 21 ± 1.1 yrs Gender: 7♀; 7♂	Right RF	Intervention group (n = 7): 3 weeks, 9 sessions of 4 sets × 6-8 reps at 75% - 80% of 1-RM of single leg squats. Tempo: 3" concentric – 4" eccentric	CSE during contraction and SICI at rest	CSE: ↑* 62.3% SICI: ↓* 21.3%	↑* 35.4%	6
			Control group (n= 7): Control period without training	CSE during contraction and SICI at rest	CSE and SICI: ↔	↔	

Table 3. Chronic effects of dynamic (n = 10) and static (n = 2) RT on ipsilateral TMS measurements and untrained limb strength.

Study	Sample	Muscle group	Intervention	Neurophysiological measures	Main outcomes	Δ strength of untrained limb	Quality
Latella et al. (2012)	n = 18 (all RLD) Age range: 18-35 yrs Gender: 4♀; 14♂	Right RF	Intervention group (n = 9): 8 weeks, 24 sessions of 3 sets × 4-8 reps progressed from 78 to 88.5% of 1-RM (single leg press). Tempo: Unknown	CSE and SP during contraction	CSE: ↔ SP: ↓* 18%	↑* 20.4%	4
			Control group (n = 9): Control period without training	CSE and SP during contraction	CSE and SP: ↔	↔	
Kidgell etal. (2015)	n = 27 (all RHD) Age: 26 ± 1.5 yrs Gender: 12♀; 15♂	Right FCR	Eccentric group (n = 9): 4 weeks, 12 sessions of 4 sets × 6-8 reps of maximal eccentric wrist flexions at 0.34 rad·s^{-1}	CSE, SP, and SICI during isometric, eccentric and concentric contractions	CSE during eccentric contractions: ↑* 51%, and ↔ during isometric and concentric contractions SICI during isometric contraction: ↓* 32% SP during isometric contraction: ↓* 27% SP and SICI during concentric and eccentric contractions: ↔	Isometric: ↑* 43% Eccentric: ↑* 47% Concentric:↑* 49%	6
			Concentric group (n = 9): 4 weeks, 12 sessions of 4 sets × 6-8 reps of maximal concentric wrist flexions at 0.34 rad·s^{-1}	CSE, SP, and SICI during isometric, eccentric, and concentric contractions	CSE, SP, and SICI during isometric, concentric, and eccentric contractions: ↔	Isometric:↔ Eccentric: ↔ Concentric: ↑* 28%	
			Control group (n = 9): Control period without training	CSE, SP, and SICI during isometric, eccentric, and concentric contractions	CSE, SP, and SICI during isometric, concentric, and eccentric contractions: ↔	Isometric: ↔ Eccentric:↔ Concentric: ↔	
Urbin et al. (2015)	n = 4 (3 RHD, 1 LHD) Age: 50 ± 11.8 yrs Gender: 3♀; 1♂	Right and left EDC	Intervention period (n = 4): 4 weeks, 16 sessions of 6 sets × 6-8 reps at 80% of 1-RM of dynamic wrist extension. Tempo: 3" concentric – 4" eccentric	CSE and SP during contraction	CSE and SP: ↔	↑* 19% (from 10.5 Kg to 12.5 Kg)	1
			Control period (n = 4): 4 weeks without training just before training intervention	CSE and SP during contraction	CSE and SP: ↔	↔	

Table 3. Chronic effects of dynamic (n = 10) and static (n = 2) RT on ipsilateral TMS measurements and untrained limb strength.

Study	Sample	Muscle group	Intervention	Neurophysiological measures	Main outcomes	Δ strength of untrained limb	Quality
Coombs et al. (2016)	n = 23 (all RHD) Age range: 18-36 yrs Gender: 12♀; 11♂	Right or Left ECR	Right hand training group (n = 8): 3 weeks, 9 sessions of 4 sets × 6-8 reps at 70% of 1-RM of dynamic extension of wrist (with dumbbell).Tempo: 3" concentric – 4" eccentric	CSE, SICI, and SP during contraction	CSE and SICI: ↔ SP: ↓* 14-27%	↑*10% (from 7.90 ± 2.90 Kg to 8.74 ± 3.10 Kg)	7
			Left hand training group (n = 8): 3 weeks, 9 sessions of 4 sets × 6-8 reps at 70% of 1-RM of dynamic extension of wrist (with dumbbell).Tempo: 3" concentric – 4" eccentric	CSE, SICI, and SP during contraction	CSE, SICI, and SP: ↔	↑* 15% (from 8.80 ± 2.70 Kg to 10.20 ± 3.60 Kg)	
			Control group (n = 7): Control period without training	CSE, SICI, and SP during contraction	CSE, SICI, and SP: ↔	↔	
Manca et al. (2016)	n = 34 (all RHD); Age: 25.5 ± 6.0yrs Gender: 11♀; 23♂	Right FDI	Intervention group (n=17): 4 weeks; 12 sessions of 5 sets × 10 reps of MVC of isometric key pinching. Tempo: 5" contraction – 5" rest	CSE, SICI, ICF, and IHI at rest	CSE, SICI, ICF, and IHI: ↔	↑* 7.7% (from 20.6 ± 4.2 Kg to 22.2 ± 4.6 Kg)	6
			Control group (n = 17): Without training	CSE, SICI, ICF, and IHI at rest	CSE, SICI, ICF, and IHI: ↔	↔	
Zult et al. (2016)	n = 24 (all RHD) Age: 27 ± 10 yrs Gender: 5♀; 19♂	Right FCR	Non mirror training group (n = 12): 3 weeks, 15 sessions of 6 sets × 8 reps at 80% of MVC of dynamic wrist flexions without any visual feedback of the untrained wrist. Tempo: Unknown	CSE, SICI, SP, and IHI at rest, and during trained limb contraction	CSE and SICI at rest: ↔ CSE during trained limb contraction: ↑*49-55% SICI during trained limb contraction: ↓* 28-45% SP: ↔ IHI: ↓* 15%	↑* 34% (from 9.0 ± 3.0 N·m to 14.4 ± 2.5 N·m)	6
			Mirror training group (n = 12): 3 weeks, 15 sessions of 6 sets × 8 reps at 80% of MVC of dynamic wrist flexions with mirror visual feedback of the untrained wrist. Tempo: Unknown	CSE, SICI, SP, and IHI at rest, and during trained limb contraction	CSE and SICI at rest: ↔ CSE during trained limb contraction: ↑*49-55% SICI during trained limb contraction: ↓* 28-45% SP: ↓* 15% IHI: ↑* 11	↑* 61% (from 9.5 ± 3.7 N·m to 12.7 ± 4.4 N·m)	

Table 3. Chronic effects of dynamic (n = 10) and static (n = 2) RT on ipsilateral TMS measurements and untrained limb strength.

Study	Sample	Muscle group	Intervention	Neurophysiological measures	Main outcomes	Δ strength of untrained limb	Quality
Mason et al. (2017)	n = 10 (all RHD) Age range: 18-35 yrs Gender: 10♀; 10♂	Right BB	Intervention group (n = 10): 3 weeks, 9 sessions of 4 sets × 6-8 reps at 80% of 1-RM of unilateral dynamic elbow flexion. Tempo: 3'' concentric – 4'' eccentric	CSE and SP during contraction	CSE: ↑* 25% SP: ↓* 15.3%	↑* 23%	7
		Right BB	Control group (n = 10): Control period without training	CSE and SP during contraction	CSE and SP: ↔	↔	
Leung et al. (2018)	n = 32 (3 LHD, 29 RHD) Age: 26.4 ± 6.9 yrs Gender: 17♀; 15♂	Dominant BB	Metronome paced group (n = 11): 4 weeks, 12 sessions of 4 sets × 6-8 reps at 80% of 1-RM of unilateral dynamic elbow flexion. Tempo: 3'' concentric – 4'' eccentric	CSE and SICI during contraction	CSE: ↑* 106% SICI: ↓* 47%	↑* 16%	6
			Self-paced group (n = 11): 4 weeks, 12 sessions of 4 sets × 6-8 reps at 80% of 1-RM of unilateral dynamic elbow flexion. Preferred tempo	CSE and SICI during contraction	CSE and SICI: ↔	↑* 13%	
			Control group (n = 10): Control period without training	CSE and SICI during contraction	CSE and SICI: ↔	↔	

Statistically significant change $P < 0.05$; RHD: Right hand dominant; LHD: Left hand dominant; RLD: Right leg dominant; BB: Biceps brachialis; RF: Rectus femoris; FCR: Flexor carpi radialis; EDC: Extensor digitorum communis; ECR: Extensor carpi radialis FDI: First dorsal digitorum; RM: Repetition maximum; MVC: Maximum voluntary contraction; CSE: Corticospinal excitability; IHI: Interhemispheric inhibition; SICI: Short interval intracortical inhibition; ICF: Intracortical facilitation; SP: Silent period.

6.4.4 Primary outcomes

6.4.4.1 Acute studies

Measured at rest (401, 405) or during a weak test contraction of the untrained muscle pair (76, 408), ipsilateral CSE increased by 54.9% (± 16.4) (76, 405), decreased by 26 to 60.6% (401, 405) or did not change (76, 408) after an acute session of dynamic unilateral RT.

In acute studies using isometric training contractions, ipsilateral CSE, measured at rest (325, 402, 403, 407, 409) or during a weak test contraction of the trained (406) or untrained muscle pair (404) remained unchanged or decreased by 15% five to 15 minutes after the intervention (407).

Ipsilateral SICI measured at rest (325, 403, 407, 409) or while contracting the untrained muscle pair (76) did not change or decreased by 39.2% (± 6.62) (76, 407) after acute bouts of unilateral RT.

Ipsilateral ICF decreased by 27.3-96.7% (403, 409) immediately after training or did not change (325, 407, 409).

IHI in the untrained muscle pair during low-intensity isometric contraction did not change (408), while it was acutely diminished (8.8 ± 3.9%) when measured at rest (325).

6.4.4.2 Chronic studies

Ipsilataeral CSE increased (74, 89, 90, 109, 325, 335-337) or remained unchanged (39, 327, 332, 336, 410) after periods of chronic unilateral RT when measured at rest (89, 325, 332) or while the trained (89, 325) or untrained muscle was weakly contracted (39, 74, 90, 109, 327, 332, 335-337, 410). After chronic unilateral RT, ipsilateral CSE increased by 27.7% (± 34.3). This mean change is based on data in nine studies that measured ipsilateral CSE at 20% of maximal stimulator output above AMT (39, 74, 327, 335) and 130% of AMT intensity (336, 337) during low intensity contraction of the untrained muscle, and also on changes in ipsilateral CSE measured at 120% of the AMT intensity during trained limb contraction (89) or at rest (325, 332).

Ipsilateral SICI was measured at rest (89, 325, 332) and while subjects contracted the trained (89) or untrained muscle pair (90, 109, 327, 335, 336). SICI in

the ipsilateral M1 decreased by 32.9 ± 10.7% (89, 90, 109, 335, 336) or remained unchanged (89, 109, 325, 327, 332, 336) after chronic unilateral RT. Additionally, SP was unchanged (74, 410) or became shorter by 21 to 26 ms, (39, 337) after chronic unilateral RT. SP revealed large variation because it remained unchanged or shortened depending on contraction type (109), limb dominance (327) or visual feedback (89) used in the chronic unilateral RT.

IHI measured at rest decreased (30.9 ± 3.8%) after 20 sessions of unilateral RT of the right first dorsal interosseous (325), increased (89) or remained unchanged after 12 sessions of unilateral RT (332). Chronic unilateral RT did not modify ICF (325, 332).

The mean CE after chronic unilateral RT was 23.3 ± 14.4%. Figure 8 shows that data from the same nine studies used to calculate mean ipsilateral CSE changes correlated r = 0.649 ($P < 0.01$) with increases in maximal voluntary force of the untrained limb.

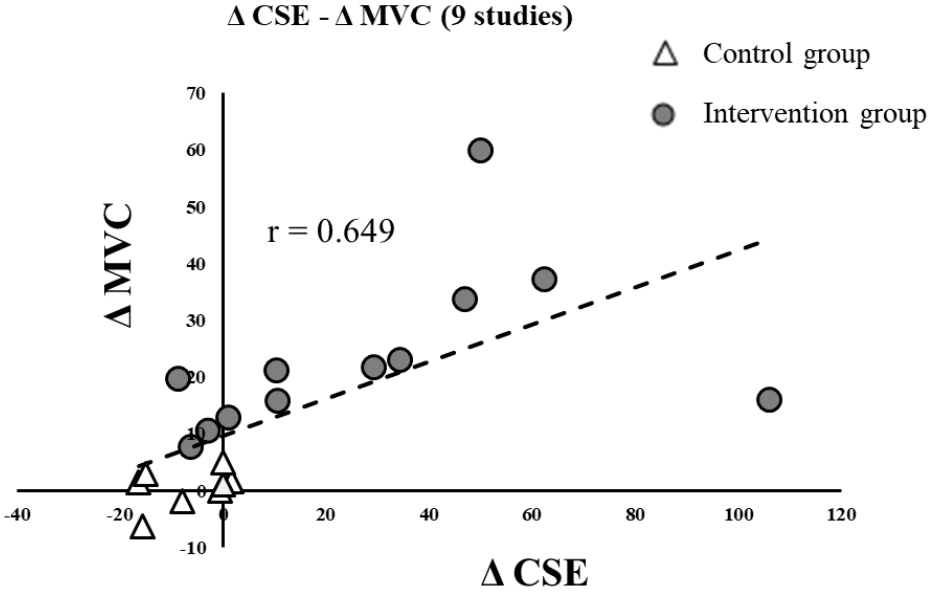

Figure 8. Correlation between changes in ipsilateral corticospinal excitability and maximal voluntary force of the untrained limb.

6.5 DISCUSSION

Results from the present review show that chronic unilateral RT leads to increased ipsilateral CSE (n = 8 studies), and reduced ipsilateral SICI (n = 5 studies), SP (n = 5 studies), and IHI (n = 1 study). Such findings partially support the cross-activation model, by which the activation of the ipsilateral brain structures by the unilateral muscle contractions during unilateral RT, serves as the training stimulus for chronic adaptations in the ipsilateral brain areas. However, such cross-activation of the ipsilateral M1 does not to lead to similar response after an acute session of unilateral RT, in which the pattern of change in ipsilateral CSE (increased, n = 2 of 11), ipsilateral SICI (decreased, n = 2 of 5), or IHI (did not change, n = 1) was much more variable.

The ipsilateral M1 adaptations after chronic unilateral RT may reflect changes in the membrane properties of the corticospinal neurons, increases in the efficacy of the excitatory synapses, a decrease in the excitability of the GABAergic inhibitory interneurons, and/or reductions in the interhemispheric inhibition input from contralateral to ipsilateral cortex (325, 335).

Such adaptations could be increasing the effectiveness of the motor command, thus contributing to CE after chronic unilateral RT. Figure 8 shows that increases in ipsilateral CSE and CE correlate $r = 0.649$ ($P < 0.01$, n = 9 studies), suggesting that the change in ipsilateral CSE could be one of the mechanisms explaining the increase in maximal voluntary force in the untrained limb (39, 74, 89, 325, 327, 332, 335-337). However we must be cautious with this interpretation because it is hampered by a lack of correlation reported in individual studies between changes in ipsilateral CSE and CE (336, 337), and whether or not the level of ipsilateral CSE at baseline drives this relationship (411). Indeed, a recent review reported zero association between skill learning and changes in CSE based on individual data (n = 251) from 11 studies (412). In addition, results revealed high variability in the ipsilateral M1 excitability measured after a bout or a period of unilateral RT, with several chronic studies (n = 4 for ipsilateral CSE, n = 3 for SICI, n = 2 for SP, and n = 2 for IHI) reporting no changes in measures of ipsilateral M1 excitability. However, the source of this variation may be related to differences in the training variables between studies such as the type of contraction, the intensity of training, the degree of fatigue or the external pacing of the movement, as discussed underneath.

6.5.1 Contraction type and intensity

Cross activation of the ipsilateral M1 is greater during dynamic eccentric than dynamic concentric or static unilateral voluntary muscle contractions, leading to higher ipsilateral CSE, and reduced ipsilateral SICI, and IHI in the ipsilateral M1 (112, 113). It is probably that this higher cross-activation is due to greater neural resources needed for programming and planning eccentric contractions in comparison to static or concentric contractions (172), or because of inhibitory and facilitatory influences from the dorsal premotor and posterior parietal cortices in the involved M1 and the ipsilateral M1 (413, 414). Therefore, if unilateral eccentric muscle contractions lead to greater activation of the ipsilateral brain areas in comparison to static or pure concentric contractions, following the cross-activation model it is possible that eccentric or mixed (concentric and eccentric) contractions during unilateral RT could serve as a greater training stimulus for ipsilateral M1 adaptations. In this regard, results from the acute studies show that those sessions that increased ipsilateral CSE and reduced SICI comprised dynamic contractions (76, 405). Furthermore, the chronic studies reporting reductions in SICI and SP (39, 89, 90, 109, 327, 335-337) used dynamic unilateral RT. For example, CE after chronic unilateral RT was greater after eccentric compared with concentric training and was accompanied by greater increases in ipsilateral CSE, and reductions in ipsilateral SICI and SP duration (109). It thus seems that chronic unilateral RT comprising a movement element through eccentric or concentric muscle contractions compared with static efforts, contributes to increases in ipsilateral M1 excitability.

Still, the results are not entirely consistent, as some acute (408) and chronic studies (39, 74, 109, 327, 410) found no effects of dynamic unilateral RT on measures of ipsilateral M1 excitability. Furthermore, a recent meta-analysis observed no discernible effects of contraction type on chronic ipsilateral CSE and SICI adaptations (63). We thus tentatively suggest that the specific modulation of the ipsilateral M1 during dynamic, in particular eccentric voluntary muscle contractions, due to higher neural resources needed and the differential activation of brain areas subserving the ipsilateral M1 (112), is likely to increase the ipsilateral M1 excitability. However, factors other than contraction type may also

contribute to changes in ipsilateral M1 excitability after acute and chronic unilateral RT.

Training intensity can be one such training variable. Indeed strength gains seem to scale with contraction intensity used in RT (96). Likewise, ipsilateral CSE parametrically increases (199), and ipsilateral SICI and IHI decrease during high intensity contractions (115). Therefore, based on the cross-activation model, the higher ipsilateral brain activation because of the repeated high intensity contractions during unilateral RT, could serve as a greater training stimulus for ipsilateral M1 adaptations in comparison with lower intensities. This prediction is compatible with the greater ipsilateral M1 adaptations and CE occurring after chronic eccentric-based unilateral RT compared to concentric unilateral RT (109), because it is known that the torque performed during maximal eccentric contractions is 20-30% higher than during concentric actions (415). However, a direct comparison of the effect of the intensity of chronic unilateral RT in the ipsilateral M1 adaptations with the included studies is not possible because all used high intensities between 70% and 100% of RM (dynamic studies) or MVC (static studies). Regarding acute studies, few showed an increase in ipsilateral CSE or a reduction in ipsilateral SICI without a clear relationship of those changes with the intensity used during training. Therefore, although high intensity muscle contractions evoke greater ipsilateral brain activation (199), an experimental confirmation of the effect of this phenomenon in ipsilateral M1 adaptations and CE is lacking.

6.5.2 Effect of fatigue

During prolonged submaximal contractions, α-motoneuron recruitment increase because of an increase in the excitatory drive to the motor units of the training muscle in compensation for reductions in muscular efficiency (235). In addition, the amount of fatigue in the training limb is, together with the intensity, an important factor determining the presence and magnitude of associated EMG in the contralateral homologous muscle (207). Because the associated EMG is probably a result of descending volleys generated by the cross-activation of the ipsilateral M1 (208), it is likely that contractions leading to muscle failure (or near failure) would not only increase associated EMG but also ipsilateral M1

activation. Therefore, according to the cross activation hypothesis (67), the higher concurrent activation of the ipsilateral M1 with the contralateral M1 during fatiguing contractions could serve as a better training stimulus for increases in ipsilateral M1 excitability and by extension for CE.

However, contrary to this hypothesis, Humphry, Lloyd-Davies (405) observed a reduction of ipsilateral CSE when healthy volunteers performed an acute bout of dynamic unilateral RT to failure. Furthermore, they also found ipsilateral CSE facilitation when the set was performed until 25% of the volume needed to failure. In addition, other studies found that ipsilateral CSE decrease when subjects exercised to the point so that they were unable to perform the movement (401, 405) or exert any force (407). With regards to other variables like ipsilateral SICI, IHI, and ipsilateral ICF, no clear differences were found depending on the level of fatigue achieved during the training session (i.e.: leading or not to muscle failure). Furthermore, no studies have addressed yet the neuroplastic changes produced by chronic unilateral RT leading or not to muscle failure, which in terms of a regular weightlifting program is an essential variable (307). Therefore, more research is needed to determine the effects of fatigue in the training limb caused by acute and chronic unilateral RT on ipsilateral M1 adaptations and CE.

6.5.3 Externally- vs. self-paced training

Practice of a simple or a skilled task with external compared with internal pacing of the movement leads to higher facilitation of CSE of the trained side (416, 417). The greater increase in CSE it is thought to be a consequence of the repeated arrival of afferent auditory inputs from the auditory cortex (through projections from the ipsilateral premotor and supplementary motor cortex to the M1) synchronized with the activation of corticospinal cells in the M1 during the muscle contractions, that lead to increased synaptic efficacy according to Hebbian principles (418). Furthermore, intracortical inhibition is decreased during synchronized contractions to an external auditory signal (419) and remains diminished after an acute or chronic period of externally paced unilateral RT in the trained limb (76, 336).

Results from recent studies suggest that not only contralateral M1 but also ipsilateral M1 plasticity is affected by the pacing strategy during unilateral RT, with externally paced movements leading to greater increases in ipsilateral M1 excitability and reductions in SICI after both, acute and chronic unilateral RT (76, 336). However, externally paced chronic unilateral RT also produced mixed results with respect to ipsilateral M1 adaptations, as in some studies there were no changes in ipsilateral M1 excitability or SP decreased after chronic unilateral RT with the dominant limb but remained unchanged after non-dominant limb training despite the inclusion of externally paced unilateral RT (327). Therefore, the data are mixed in support of greater increases in ipsilateral M1 excitability after externally- vs. internally paced unilateral RT. Furthermore independent of its effect on ipsilateral M1 adaptations, there is no evidence to suggest that CE is preferentially greater after externally- vs. internally-paced chronic unilateral RT. In fact, a recent study reported that externally- vs. internally-paced chronic unilateral RT, did result in higher ipsilateral M1 adaptations, however such changes were not coupled with greater strength increases in the trained and the untrained limb when compared to internally-paced training

6.6 CONCLUSIONS

In conclusion, results from the present review show a high heterogeneity in the response of the ipsilateral M1 to an acute bout, but also after a chronic period of unilateral RT. It can not be ruled out that the contradictory effects on the ipsilateral M1 could be a consequence of the methodology approach. For example, as described in the results section, one of the main variations in the measurement of ipsilateral CSE and SICI is the situation in which they were measured (during contraction or at rest). It is likely that in order to detect possible neurophysiological adaptations after a training period, the task in which measures are performed, should be similar, if not equal, to the task done during training (32). Furthermore, a more homogeneous methodology of measurements could facilitate the comparison of results between studies, thus helping to determine the differential effect of training variables like those discussed in this review on the ipsilateral M1 measurements and its relation to CE.

However, apart from the methodology approach, the high heterogeneity in the response of the ipsilateral M1 to acute and chronic unilateral RT seems to be related to the training configuration itself, which could trigger different ipsilateral M1 adaptations. In this regard, the tentative conclusion is that high intensity, eccentric or externally paced muscle contractions are the more effective training variables to increase ipsilateral M1 excitability. Notwithstanding, CE can occur in the absence of such changes whereby, the mechanism of CE examined with TMS remains unclear. Maybe structures other than ipsilateral M1 that TMS cannot probe and that are bilaterally activated during unilateral contractions, like supplementary motor area, sensory regions, prefrontal, premotor, cingulate and parietal cortices, or cerebellum (73) could also be related to CE (23, 66). However, further research should shed more light on the effects of intensity (i.e.: comparing low-load to heavy-load unilateral RT) and fatigue (i.e.: comparing unilateral RT using sets leading or not to muscle failure) on CE and its underlying neural mechanism. This is important in order to maximize the benefits of the unilateral RT as a tool to reduce asymmetries in different athletic samples, as well as in patients with orthopaedic or neurological impairments.

VII – STUDY 3

VII – STUDY 3

Training intensity-dependent increases in corticospinal but not intracortical excitability after acute strength training

7.1 ABSTRACT

The purpose of this study was to determine if the increases in CSE observed after one session of unilateral isometric strength training (ST) are related to changes in intracortical excitability measured by TMS in the in the trained and the contralateral untrained BB and if such changes scale with training intensity. On three separate days, 15 healthy young men performed one ST session of 12 sets of eight isometric contractions of the right elbow flexors at 0 (Control session), 25, or 75% of the MVC in a random order. Before and after each session separated at least by one week, MEP amplitude, SICI, contralateral SP and ICF generated by TMS, were measured in the trained and the untrained BB. Compared to baseline, MEPs recorded from the trained BB increased by ~47% after training at 75% of MVC ($P < 0.05$) but not after training at 0% (~4%) or 25% MVC (~5%, both $P > 0.05$). MEPs in the untrained BB and SICI, SP, and ICF in either BB did not change. Therefore, acute high- but not low-intensity unilateral isometric ST increases CSE in the trained BB without modifications in intracortical inhibition or facilitation. Thus, increases in corticospinal neurons or α- α-motoneuron excitability could underlie the increases in CSE. Regardless of contraction intensity, acute isometric ST did not modify the excitability of the ipsilateral M1 measured by TMS.

7.2 INTRODUCTION

Strength training (ST) is an effective means to increase maximal voluntary MVC force and muscle mass (39, 40, 49). The chronic increases in MVC force after ST are usually accompanied by neural adaptations at a supraspinal (39, 40) and spinal level (49). However, little is known about how fast such neural adaptations occur after beginning a ST program. Recent studies have shown that even just a single ST session can evoke spinal and cortical modulations (75, 77, 420) as determined by electrical stimulation at the mastoid process and TMS over the contralateral M1, respectively. Indeed, acute ST increased the synaptic efficacy of neural transmission in the corticospinal tract, α-motoneuron excitability and/or contralateral M1 excitability (77, 420). Furthermore, there are indications for contraction intensity-dependent effects of ST on CSE measured by TMS because high versus low training loads produced more pronounced and longer-lasting changes in neuronal excitability (420). However, changes in spinal excitability measured by cervicomedullary electrical stimulation did not produce such intensity-dependent effects (420). This suggests that the contralateral M1 is more sensitive to the intensity of muscle contraction used in acute ST compared to α-motoneurons, supporting the hypothesis that short-term neural adaptations to ST occur at the supraspinal level.

A dose-response relationship in the responses to corticospinal but not spinal stimulation following acute ST could reflect the involvement of contralateral M1 circuits (76). Intracortical circuits can inhibit or facilitate the responses to TMS in the contralateral M1 (144). GABA is the main inhibitory neurotransmitter in M1, which acts mainly through interneurons with GABA-A receptors, responsible for fast synaptic inhibition, and GABA-B receptors, responsible for slower but longer-lasting inhibition (421). Both forms of inhibition can be measured with paired- and single-pulse TMS, respectively (140, 145). Although both forms of inhibition are mediated by different populations of interneurons, these project to higher-threshold circuits that activate the corticospinal tract neurons, ultimately reducing M1 excitability (144). Therefore, although there is still no evidence of a relationship between chronic changes in intracortical inhibition and the force of a muscle contraction, decreases in the efficacy of those inhibitory intracortical

circuits can release M1 from inhibition, increasing M1 excitability, the efficacy of the motor command, and the drive to muscles to contract more forcefully. In fact, chronic ST tends to decrease SICI and SP duration (40, 422), suggesting that a release of intracortical inhibition could be one mechanism underlying the chronic increases in M1 excitability and in the effectiveness of the motor command to increase MVC force. However, the time course of such adaptations is unclear because results from acute studies are inconsistent (76, 260, 261, 383). In addition to reductions in SICI or SP, an increase in ICF could also contribute to the increase in CSE. ICF is thought to involve corticocortical pyramidal cells with glutaminergic synapses projecting to the cortical neurons that activate the corticospinal tract (423). However, little is known about changes in ICF after an acute session of ST, with two studies showing little or no changes (260, 261).

Therefore, because spinal mechanisms cannot fully account for the changes in CSE in relation to the ST intensity (420), changes in intracortical circuits could be the main mechanisms modulating CSE. Indeed, contrary to what happens with CSE, which increases with contraction intensity (up to a limit), SICI tends to decrease with the intensity of the voluntary drive (190). We could thus expect that high- compared with low-intensity ST would have a greater potential to modify intracortical circuits, accounting for the greater responses to TMS after a single session of high- vs. low-intensity ST (420).

A unilateral voluntary muscle contraction can also activate ipsilateral brain areas (73, 115). Such cross-activation could be the source of adaptations in the untrained hemisphere, underlying increases in MVC force in the untrained homologous muscle when unilateral muscle contractions are repeated for a period of at least three weeks (39, 89, 325). However, it is unknown if, akin to the trained side (75, 77, 420), neural modulations in the untrained hemisphere are already present after just one session of ST, or if more training sessions are needed for neural changes to occur. Furthermore, because the excitability of the M1 ipsilateral to the contracting muscle increases during discrete unimanual muscle contractions in an intensity-dependent manner (70, 115), we hypothesize that acute ST would also induce intensity-dependent changes in the ipsilateral M1 excitability.

Therefore, the purpose of the present study was to determine if the increase in CSE after one session of ST is related to changes in SICI, SP, and ICF and if

such changes would occur in an intensity-dependent manner in the trained and the untrained BB. A detailed understanding of the time course of adaption to ST and its dependency on contraction intensity has important implications for patients with neuromuscular conditions and older adults who might be unable to participate in high-intensity ST protocols.

7.3 MATERIAL AND METHODS

7.3.1 Participants

Healthy, right-handed, and recreationally active men (2-3h per week of recreational sports activities or aerobic training, age, 23.93 ± 4.65 years, n = 15) with no reported contraindications to TMS and not currently taking any medications volunteered to participate in the study. One week before the start of the experiments, participants were familiarized with peripheral nerve stimulation, TMS, and MVC protocols. Participants were asked to refrain from consuming alcoholic or caffeinated beverages and from exercising for at least 24h before each experimental session. The Institutional Review Board of the Catholic University of Murcia approved the protocol. Written informed consent was obtained from all participants before the start of the study. The experiments were performed in accordance with the latest version of the declaration of Helsinki.

7.3.2 Experimental procedures

Each subject completed in a random order each of the three ST sessions at zero (CON), 25, and 75% of MVC, one intensity per session, with each session separated by one week. The CON session consisted of 20 minutes of rest in the posture used in training. ST sessions consisted of 12 sets of eight isometric right elbow flexor contractions ramped to 25% or 75% of MVC over two seconds. After reaching the target force, participants relaxed the elbow flexors and rested for four seconds. There was one minute of rest between sets.

Before (PRE) and after (POST) each intervention, one block of measurements with TMS (single- and paired-pulse) and brachial plexus stimulation was obtained from both arms during a low-level contraction of 5% of

MVC. POST measurements started always in the left arm around 30 seconds after the last training set. Each block of measurement consisted of eight M_{max}), 20 single-pulse MEPs and 40 paired-pulse stimulations (20 for SICI and 20 for ICF). All stimuli were separated by five seconds, and 30 seconds of rest were given after 15 pulses to avoid fatigue, so each block lasted for ~7 minutes. Additionally, five single-pulse MEPs at 120% of AMT ($MEP_{25\%}/M_{max}$) and its respective SP were obtained in both BBs during 3-second-long contractions at 25% of MVC immediately before training or control period and at POST (approximately 10-15 minutes after training or control period ended) (see Figure 9.). Single pulse stimulation during 25% vs. 5% of MVC contractions allowed us to obtain clearer SPs.

Before measurements, participants performed three MVCs with each arm separately. MVCs lasted for three seconds with 120 seconds of rest between trials. The posture during MVC tests and main measurements was identical. All trials were measured with two force transducers (Neurolog System, Digitimer, Welwyn Garden City, United Kingdom) firmly attached to the left or right wrist with a rigid strap. The highest MVC in each arm was used to determine the subsequent target force during measurements (5% and 25% of MVC) and training (25% or 75% of MVC).

7.3.3 Set-up

During testing participants sat in a chair in front of a table with both shoulders flexed at 90º and the elbows flexed with forearms supinated and vertical (Fig. 9). In this position, both forearms were fastened with a rigid strap to a force transducer (NL63-200 Kg; Digitimer, Welwyn Garden City, United Kingdom) to measure voluntary force, which was displayed on a computer monitor in front of the participants.

EMG was recorded from the right and left BB with Ag-AgCl surface electrodes in a belly-tendon montage (5-8 cm inter-electrode distance). EMG was amplified (x200 or x300 depending on the M_{max} amplitude), band pass filtered (10-1000Hz) and sampled (2kHz) with a Digitimer d440 isolated amplifier (Digitimer, Welwyn Garden City, United Kingdom). Force recordings were band-pass filtered (5-2500 Hz), amplified (x2500) and sampled at 2kHz using a Neurolog System (Digitimer, Welwyn Garden City, United Kingdom). Both EMG and force recordings were simultaneously collected using an analog-digital board CED Micro1401-3 (Cambridge Electronic Design, Cambridge, UK) for further analysis.

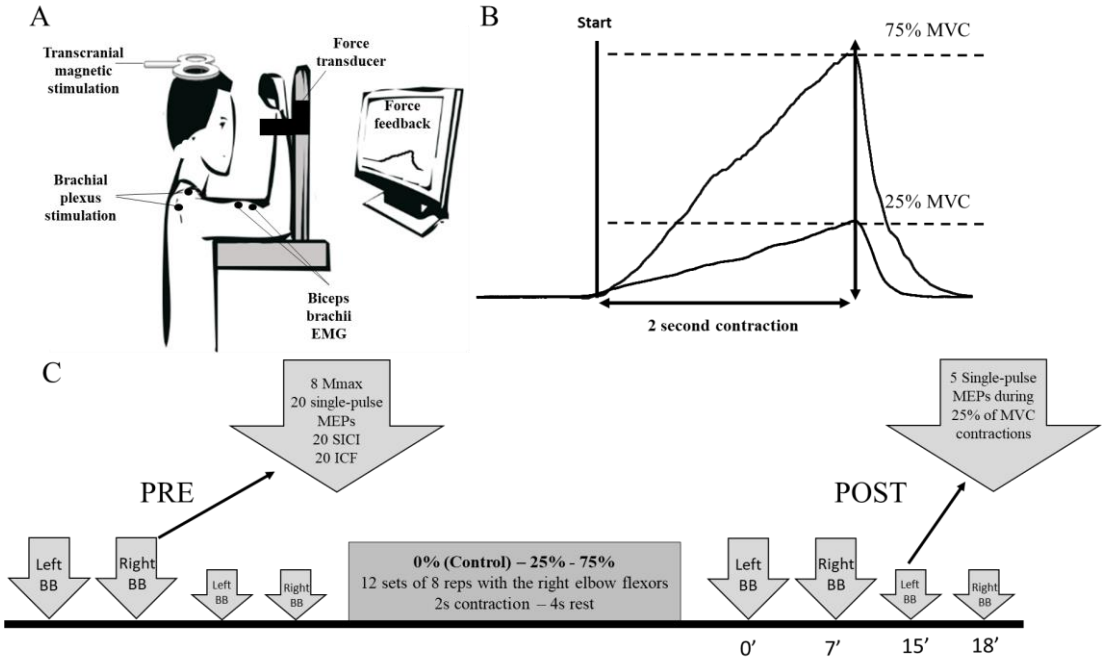

Figure 9. Schematic view of the set-up and protocol. (A) Participants completed the experiment seated with the elbow and the shoulder flexed to 90º. Visual feedback of the force was provided on a screen in front of the participants. (B) Raw traces of a contraction from each training session from a representative subject. In each training session the participants steadily contracted their BB until the required intensity marked with a horizontal line during a two second period identified with two vertical bars. (C) Motor evoked potentials were obtained before (PRE) and after (POST) each session (CON, 25, or 75% of MVC).

7.3.4 Brachial Plexus stimulation

For recording the M_{max} in each BB, single pulse stimulation (200μs duration) was delivered to the brachial plexus with a DS7AH constant current electrical stimulator (Digitimer, Welwyn Garden City, United Kingdom). The cathode (pre-gelled Ag-AgCl electrodes) was positioned in the supraclavicular fossa and the anode on the acromion. After defining the stimulation intensity needed to evoke the M_{max} in each BB, the intensity was set to 120% of this value for the measurements (range 42 - 186 mA).

7.3.5 Transcranial Magnetic Stimulation

Single- and paired-pulse TMS was delivered to left (contralateral M1) and right (ipsilateral M1) motor cortices with a figure of eight coil (70mm diameter) connected to two DuoMag (Rogue Resolutions Ltd., UK) magnetic stimulators. The coil was oriented with the handle at ~45º postero-laterally to the midline and the optimal stimulation location in each M1 was obtained by exploring the estimated center of the BB motor cortical representation. The point where stimulation produced the largest MEP in the contralateral BB was marked directly on the scalp with a permanent marker. AMT was defined as the lowest stimulation intensity needed to obtain three out of five MEPs of a peak-to-peak amplitude greater than 200μV during a 5% MVC force, displayed as target on the monitor in front of the participant. To measure SICI and ICF, a paired-pulse protocol was used in which the CS and the TS set at 80% and 120% of the AMT, respectively. The interstimulus interval was set to 3ms (SICI) and 10ms (ICF).

7.3.6 Data analysis

The peak-to-peak amplitudes of M_{max} and MEPs were measured. MEP amplitudes were normalized to M_{max} within each measurement block and averaged ($MEP_{5\%}/M_{max}$ and $MEP_{25\%}/ M_{max}$). Pre-stimulus EMG_{RMS} activity was determined in a 150ms window prior to each electrical or magnetic stimulus. Trials with EMG_{RMS} larger or lower than the mean of each measurement block ± 2SDs were removed from the analysis. The SP duration was quantified as the time

between the stimulus and the time at which the post-stimulus EMG returned to the 50% of the mean of the pre-stimulus (150ms time-window) background EMG activity (424).

7.3.7 Statistics

All data were first screened for normality using a Kolmogorov-Smirnov test. Inter-session reliability of baseline M_{max}, single-, and paired-pulse TMS responses across sessions was determined using intra-class correlation coefficients (ICC (2, 1) two-way mixed effect model) with 95% confidence intervals (95% CIs). The ICC was interpreted with values below 0.5 indicating low reliability, values between 0.5 and 0.75 indicating moderate reliability, values between 0.75 and 0.9 indicating good reliability, and values higher than 0.90 indicating excellent reliability (391). Then, a two-way RM-ANOVA was performed with TIME (PRE and POST) and INTENSITY (CON, 25% and 75%) as factors for pre-stimulus EMG_{RMS}, M_{max}, $MEP_{5\%}/M_{max}$, $MEP_{25\%}/ M_{max}$, SP, SICI and ICF. Limb was not included as a factor in the RM-ANOVA because post measurements in the trained and the untrained were not simultaneous (immediately after versus ~7 minutes after, respectively). If sphericity was violated (Mauchly's test), degrees of freedom were corrected by Greenhouse-Geisser estimates of sphericity. When a non-significant main effect or interaction had a medium ES ($\eta_p^2 > 0.13$), paired comparisons and Cohen's d effect sizes were also computed. Effect sizes are presented as partial eta square values (η_p^2; small: 0.02; medium: 0.13; large: 0.26). Unless indicated otherwise, data are reported as mean ± standard deviation. SPSS 20.0 software (SPSS, Chicago, Illinois) was used for statistical analysis. Statistical significance was set at $P \leq 0.05$.

7.4 RESULTS

7.4.1 Reliability

Inter-session reliability for M_{max}, MEP5%/M_{max}, SICI (%TS), ICF (%TS), SP, and MEP25%/M_{max} was good to excellent (ICC = 0.79 to 0.94, Table 4) in the trained and the untrained BB.

Table 4. PRE measurements inter-session reliability of M_{max}, $MEP_{5\%}$/ M_{max}, SICI, ICF, SP and $MEP_{25\%}$/ M_{max}.

	Trained Inter-Session ICC (95% CI)	**Untrained Inter-Session ICC (95% CI)**
M_{max}	0.90 (0.77, 0.96)	0.83 (0.60, 0.94)
$MEP_{5\%}$/ M_{max}	0.80 (0.52, 0.90)	0.82 (0.56, 0.93)
SICI (%TS)	0.82 (0.58, 0.93)	0.94 (0.85, 0.98)
ICF (%TS)	0.86 (0.66, 0.95)	0.85 (0.64, 0.94)
SP	0.79 (0.52, 0.92)	0.89 (0.73, 0.96)
$MEP_{25\%}$/ M_{max}	0.91 (0.78, 0.97)	0.92 (0.82, 0.97)

ICC: Intraclass correlation coefficient; CI: Confident interval; M_{max}: maximal compound muscle action potential; MEP: Motor evoked potential; SICI: Short-interval intracortical inhibition; ICF: Intracortical facilitation; SP: Silent period.

7.4.2 Trained side

One subject was excluded from the statistical analysis only for the SICI variable because a consistent facilitation of more than 40% in both BBs. Pre-stimulus EMG_{RMS} remained constant during all training sessions (See Supporting information 1 (Annex 1)). MEP5%/M_{max} amplitudes increased by +46.7% (P = 0.04, ES = 0.43, 95% CI = 0.31, 0.58) only after ST at 75% MVC but not after ST at 25% MVC (+4.8%, P = 0.44, ES = 0.08, 95% CI = -0.18, 0.25) or CON (+4.4%, P = 0.76, ES =

0.04, 95% CI = -0.38, 0.36) (Figure 10). Baseline (PRE) MEP5%/M_{max} amplitudes were equal between sessions (CON vs 25% P = 0.46, CON vs 75% P = 0.99, 25% vs 75% P = 0.19), however training at 75% of MVC produced higher post-training MEP5%/M_{max} amplitudes than the CON session (P = 0.04, ES = 0.32, 95% CI = -0.01, 0.77) and revealed a trend towards significance compared to 25% session (P = 0.06, ES = 0.54, 95% CI = 0.29, 0.87).

A single session of ST at 0, 25, and 75% MVC did not affect MEP25%/M_{max}, SP, ICF and M_{max} (Supporting information 1 (Annex 1)). However, although RM-ANOVA did not show significant effects or interactions for SICI, there was a medium effect size for the Time*Session interaction (P = 0.09, $\eta p2$ = 0.17) that revealed a small increase in SICI after the 75% of MVC ST session (from 76.8% to 69.1% of TS, P = 0.01, ES = -0.26, 95.0% CI = -0.41, -0.13).

7.4.3 Untrained side

Pre-stimulus EMG_{RMS} remained constant during all training sessions. A single session of ST at 0, 25, or 75% MVC did not modify MEP5%/M_{max}, MEP25%/M_{max}, SP, SICI, ICF and M_{max} in the untrained BB (See Supporting information 2 (Annex 2)).

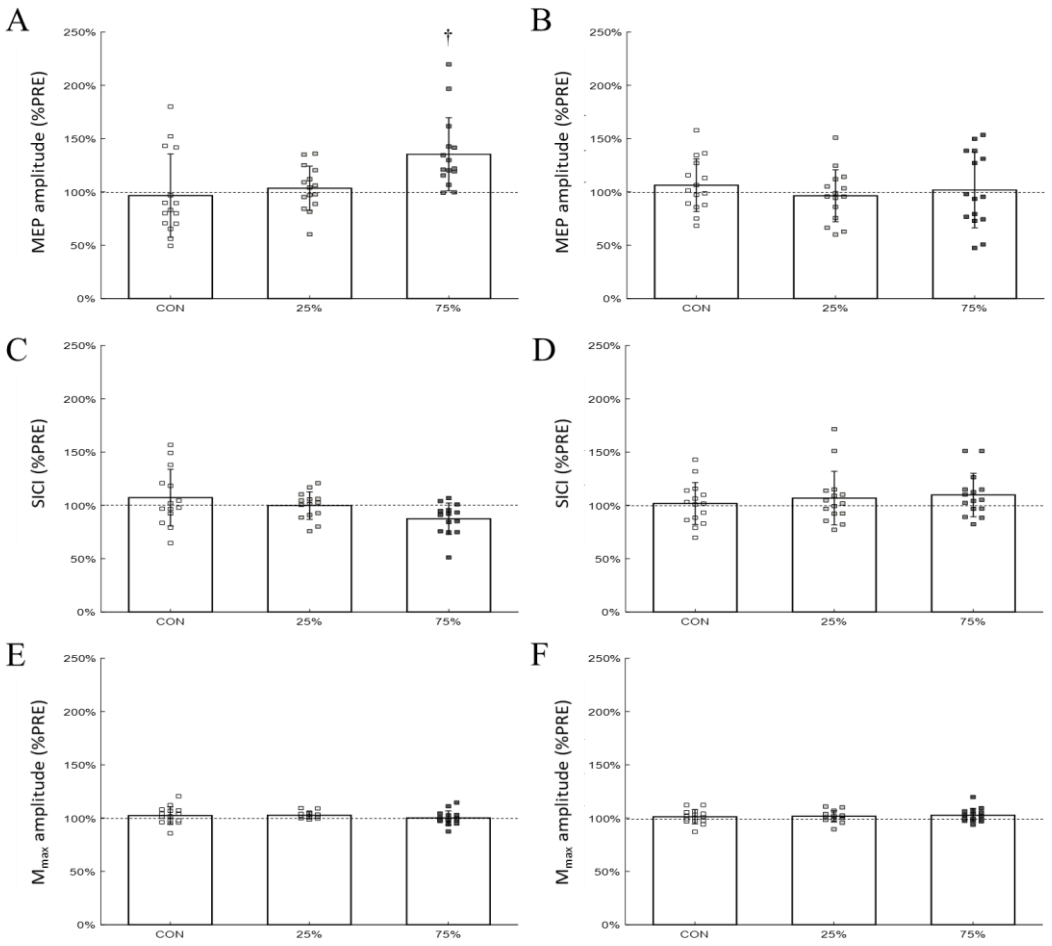

Figure 10. MEP5%/M_{max}, M_{max}, and SICI change after strength training (n = 15). Left panel shows the change (mean ±SD) in the MEP5%/M_{max} (A), SICI (C) and M_{max} (E) of the right trained BB after the ST sessions performed at 25% and 75% of the MVC and the CON condition. Right panel shows the change (mean ±SD) in the MEP5%/M_{max} (B), SICI (D) and M_{max} (F) of the left untrained BB after the ST sessions performed at 25% and 75% of the MVC and the CON condition. (†) shows a statistically significant difference ($P < 0.05$) to PRE values.

7.5 DISCUSSION

We determined the effects of acute unilateral isometric ST of the right elbow flexors at 0, 25, and 75% MVC on CSE, SICI, ICF and SP in the trained and untrained arm. Only acute ST training at 75% MVC did increase CSE in the trained BB measured during a 5% background MVC. Contrary to the hypothesis, the increases in CSE were not accompanied by a decline in intracortical inhibition or an increase in intracortical facilitation. The effects of a single session of ST at 0, 25, and 75% MVC was limb-specific, as no changes occurred in any of the TMS measures obtained in the ipsilateral M1.

7.5.1 Trained side

A single session of ST increases the responses to corticospinal tract stimulation at rest (75, 77, 420) or during low level isometric contractions (76, 260) suggesting, increases in cortical or α-motoneuron excitability or an increased efficacy of the corticospinal-motoneuronal synapse (77, 420). Our results are in line with previous studies by showing ~47% increase in CSE measured at 5% background MVC in the BB of the trained arm only after ST at 75% MVC. The present data confirm the previously described effect of intensity (420) by showing a 75%-MVC intensity-threshold of acute ST to produce meaningful changes in CSE, suggesting that training intensity is a determinant of acute corticospinal plasticity in response to a bout of isometric ST.

Although the coil of TMS is placed over M1, the response to single pulse TMS is not only affected by cortical neurons excitability. Single pulse TMS reflects the excitability of corticospinal neurons and interneurons projecting onto these neurons in M1 as well as the excitability of α-motoneurons in the spinal cord, the neuromuscular junctions and the muscle (126). Therefore, an increase in CSE measured by TMS could be due to changes at any or all of these structures. However, spinal mechanisms are unlikely to mediate the increases in CSE after acute ST (420). Previous studies showed that ST intensity affected CSE but not spinal excitability measured by cervicomedullary electrical stimulation (420). Furthermore, increases in corticospinal transmission and/or α-motoneuron

excitability after acute ST are not always present (257). For that reason, mechanisms other than spinal changes were proposed to explain the increases in CSE after acute ST. Increases in corticospinal neurons excitability or reductions in the efficacy of the intracortical inhibitory circuits can both increase the efficacy of the excitatory input to α-motoneurons thereby increasing the response to TMS. However, we found no reductions in GABA-A- or GABA-B-receptor mediated cortical inhibition.

Although two-way RM-ANOVA revealed a non-significant interaction between factors for SICI ($P = 0.09$, $\eta p2 = 0.17$), paired comparisons showed a small increase in SICI (i.e., reduced CS/TS ratio) after 75% of MVC ST session (from 76.8% to 69.1% of TS, $p = 0.01$, ES = -0.26, 95.0% CI = -0.41, -0.13). This small increase in SICI after high-intensity acute ST could be related to a methodological issue, i.e., the test pulse MEP size. The amount of inhibition increases with increasing test pulse MEP size (425). Because we used PRE stimulation intensity during the POST measurements, the increase in the test pulse MEP size after high-intensity ST could have led to the slight, non-significant increase in SICI. Although this could be viewed as a limitation, the efficacy of SICI is related to the population of cortical circuits activated by the test pulse (143). The variable that determines which circuits are activated by TMS is the stimulation intensity and not changes in excitability (143). Therefore, reductions in stimulation intensity to adjust the test pulse size after a ST session could act as a confounding factor by affecting the cortical circuits activated the test stimulus and reducing the estimates of SICI because of a higher contribution of early indirect-waves to the MEP, which are less affected by intracortical inhibition. Future studies should include both approaches (adjusted and not adjusted test pulse size) to further understand the effects of an acute ST session on SICI. Notwithstanding, the small increases in SICI in the present study partially agree with those from a recent meta-analysis showing that SICI is not modulated consistently following a single session of ST (265), which could be also related to different approaches used to measure SICI after a single session of ST (adjusted and not adjusted TS size).

Regarding SP, past results have been inconsistent with studies showing increases set by set during an ST session (383) and decreases (260) after an acute ST session. Here, we found no change after unilateral acute ST at a low or high intensity. These results combined with the SICI data suggest that, although

chronic ST could lead to reductions in SICI and SP (422), just a single session of isometric ST does not reduce the efficacy of the GABA-A- and GABA-B-receptor mediated inhibitory intracortical circuits projecting to the cortical excitatory neurons. Acute reductions in intracortical inhibition could be a compensatory mechanisms to diminish the effect of peripheral fatigue on force output (260). However, the ramped isometric contractions we used did not require participants to hold the target force, minimizing any peripheral fatigue (discussed below). Therefore, acute modifications in the efficacy of the inhibitory intracortical circuits could be more related to the level of peripheral fatigue attained during the training session than to the intensity of training (260). Also other ST characteristics could influence the acute modulation of the responses to TMS after a single session of ST. For example, dynamic ST paced by an audible cue leads to increased CSE accompanied by increased ICF and reduced intracortical inhibition whereas internally paced ST did not (258). This greater acute neural modulation could be related to higher auditory afferent input from the auditory cortex synchronized with the activation of corticospinal neurons during muscle contractions, which lead to an increased synaptic efficacy according to Hebbian principles (418). Thus, it seems that the acute neural modulation after an acute ST session could be affected by different ST characteristics like intensity, level of peripheral fatigue, the type of contraction or the strategy of pacing the movement or even the volume of exercise.

Therefore, combined results from the present and past studies (420) suggest that spinal mechanisms or changes in intracortical circuits are not the main mechanisms underlying the acute increase in CSE after an acute bout of ST. Then, it is likely that the increases in the net excitatory output from M1 to the muscle after an acute bout of ST are related to changes in the membrane excitability of the corticospinal neurons receiving input from the corticocortical neurons activated by the single pulse TMS.

A methodological difference between the present and past studies is that we measured corticospinal changes at 5 or 25% background MVC and not at rest. Measuring responses to TMS during contraction represents more faithfully the adaptations that occur during training compared to the same measures obtained at rest (32). The increased MEP size after training during contraction could thus reflect plasticity associated with the task unlike the CSE measured at rest.

Nevertheless, we found that a session of high- but not low-intensity ST increased the CSE of the trained arm when measured during 5% of MVC contractions to a similar extent as when CSE was measured at rest in previous studies (420) (+47% during contraction vs +76% at rest). The differences in the magnitude of change between both studies (420) could be related to differences in the size of the baseline MEPs (7.05% of M_{max} vs 4.57% of M_{max}). However in both studies the absolute increase was similar (to a 10% vs to a 8% of M_{max}). This suggests that the increased responses to TMS after training have not became more facilitated by the muscle contraction compared to rest, suggesting that acute changes after ST occurred in the intrinsic properties of the cortical neurons that could be already measured at rest. Nevertheless, we did not find any increases in CSE when measured during 25% of MVC contractions. MEP size in BB tends to be progressively facilitated up to a 40-50% of MVC (426). However, independent of contraction intensity, MEP size tends to peak at an amplitude around 60-70% of M_{max} (426). Therefore, a lack of change in MEPs during 25% of MVC after the high-intensity ST session could be related to the high baseline size of MEPs (~50%). The fact that baseline MEPs were already close to its maximum means that single pulse TMS before training already recruited almost all of the excitable cortical neurons, limiting the scope for further increases. Also, because measurements were obtained during contractions, it is unknown if spinal changes would have behaved in a similar manner as at rest (420). Therefore, a direct comparison with previous studies is not possible and we cannot discard a concomitant increase in α-motoneuron excitability contributing to the increase in CSE after high-intensity acute ST seen here. However short-term ST periods have failed to produce adaptations at the spinal level measured by cervicomedular electrical stimulation (47) and H-reflexes (43). This strengthens the support for the hypothesis that short-term increases in α-motoneuron discharge rate that lead to increases in MVC force are mediated by increases in the net excitatory input to the α-motoneuron pool from supraspinal centers (255).

Because we did not measure MVC force after ST, we cannot discard the possibility that fatigue has influenced our results. However, there is indirect evidence to suggest that fatigue was low or altogether absent. For example, we found no changes in the pre-stimulus EMG_{RMS}, suggesting that any increase in neural drive was needed to maintain the force output as a consequence of

reductions in muscle or α-motoneuron excitability. Also in a previous study with an identical training, resting M_{max} associated twitch forces did not decrease during the 30 minutes after the intervention, suggesting that there were no reductions in muscle contractile properties as a consequence of fatigue (420). Another factor that can potentially influence our results is central fatigue. The best indicator for the assessment of central fatigue is voluntary activation. Unfortunately, we did not measure voluntary activation in this study. However, as intracortical inhibition did not increase, we assume that central fatigue was low or altogether absent.

7.5.2 Untrained side

The central nervous system adapts quickly to motor practice in the trained and the untrained muscle (427). Therefore, several studies have examined if the acute changes occurring after a single session of unilateral ST in the trained hemisphere (75, 77, 260, 383, 420) would also occur in ipsilateral, untrained brain structures (76, 325). Notwithstanding, results from those studies are contradictory, with one study showing increases in CSE and reductions in SICI after a session of dynamic ST (76), whereas another study reported no effects of an acute unilateral isometric ST session on CSE, SICI, ICF and IHI of the untrained hemisphere (325). Our results agree with these latter data, showing no effects of a single session of isometric unilateral ST of the elbow flexors on TMS outcomes in the ipsilateral iM1. Furthermore, despite cross-sectional studies demonstrating that ipsilateral M1 excitability increases and intracortical inhibition decreases more during high- compared to low-intensity contractions (70, 115), our results revealed no intensity effects on the responses to TMS in ipsilateral M1 after a single session of unilateral isometric ST.

Discrepancies between the effects of a session of unilateral ST on the ipsilateral M1 could be related to the type of contractions used during training. Eccentric compared to concentric contractions activate the ipsilateral M1 more strongly (112). This higher cross-activation is probably a consequence of the greater neural resources needed for programming and planning eccentric compared with static or concentric contractions (172), or related to inhibitory and facilitatory influences from the dorsal premotor and posterior parietal cortices in

the contralateral and ipsilateral M1 (414). Another important aspect with regard to cross-activation is the intensity of a contraction. It is known that contractions need to be at moderate-high intensity to result in cross-activation of the ipsilateral hemisphere (70, 115). The slowly ramped isometric contractions used in the current study result in relatively short periods of contractions at moderate-high intensity (> 50% MVC). These short periods at moderate-high intensity might in turn have resulted in limited cross-activation during the contractions, reducing the scope for modulation of the corticospinal tract projecting to the untrained BB. Therefore, the absence of changes in the ipsilateral M1 after a unilateral isometric ST session could be related to an insufficient level of cross-activation during progressive isometric contractions, compared to unilateral dynamic ST mixing high intensity eccentric and concentric contractions.

Therefore, although ipsilateral M1 adaptations occur after chronic periods of ST (39, 89, 325), even with isometric contractions (325), the time course of those adaptations is longer than a single session, even if the intensity of ST is high. Indeed, previous studies showed that interlimb transfer of voluntary force and correlated increases in ipsilateral M1 excitability to occur might require at least 10 sessions or 500 isometric contractions (325). Therefore, it is not possible to infer the long-term effectiveness of different ST configurations (i.e.: intensity, volume, etc.) based on the effects of just one session of ST. Consequently, longitudinal studies will be needed to determine the effectiveness of different ST configurations on ipsilateral M1 plasticity. Furthermore, acute and chronic changes may occur in other ipsilateral structures that single coil TMS cannot probe that are also bilaterally activated during unilateral contractions, like supplementary motor area, sensory regions, prefrontal, premotor, cingulate, and parietal cortices, or cerebellum (73).

7.6 CONCLUSIONS

High- but not low-intensity isometric ST of the elbow flexors increased CSE in the BB when measured at a background MVC of 5%. However, such increases were not accompanied by decreases in intracortical inhibition or increases in intracortical facilitation. These results suggest that increases in corticospinal neurons or α-motoneuron excitability are the main mechanisms underlying the

increases in CSE. In contrast, no effects on CSE and intracortical circuitry occurred in the untrained hemisphere, suggesting that more than one session of unilateral isometric ST is needed to evoke adaptations in the untrained corticospinal tract independent of training intensity.

7.7 PERSPECTIVES

Peripheral and neural adaptations to ST have different time-courses. Adaptations in the central nervous system usually precede changes in the muscle and tend to underlie most of the early gains in MVC force. Therefore, it is important for coaches training healthy individuals and also patients with neuromuscular conditions or older adults, to know how modifications in training variables, such as training intensity, could affect early adaptations to ST. We show that training intensity is a key determinant of the acute increases in cortical or α-motoneuron excitability occurring in the early stages of training, which could explain the better effectiveness of chronic high-intensity ST in producing MVC force increases. However, just one session of unilateral isometric ST does not lead to acute changes in the ipsilateral M1.

VIII – STUDY 4

VII – STUDY 4

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

8.1 ABSTRACT

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±4.3y), low-load RT to failure (LLF, n=11, 21±1.3y, three sets to failure at 25% of 1RM), high-load RT to failure (HLF, n=11, 21±1.4y, three sets to failure at 75% of 1RM), and high-load RT without failure (HLNF, n=11, 22±1.5y, six sets of five repetitions at 75% of 1RM) groups. Before and after the four weeks of training, 1RM, maximal voluntary isometric force (MVIC) 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 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.

8.2 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 (428). 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 (96), volume (98), and fatigue (reaching or not muscle failure) (103, 107) to maximize RT-induced increases in maximal voluntary force. For example, it seems 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 (96). Another training variable contributing to the adaptive responses to RT is fatigue that develops during the exercise bout or set. Some studies suggest that training to concentric muscular failure, i.e., the inability to perform one further concentric repetition, could enhance RT adaptations (107) by increasing metabolic stress and motor unit activation (235). However, there is also evidence suggesting that muscle failure during training may not be necessary to increase maximal voluntary force (103).

Unilateral RT can also increase maximal voluntary force in the untrained limb, producing cross-education (CE) (67). However, unlike in the trained limb, how RT variables, including load or fatigue, affect CE is unclear (111). Because CE occurs without muscle hypertrophy, it is generally accepted that neural mechanisms underlie CE (63, 67, 325). 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 (67). This concurrent ipsilateral hemisphere activation is greater during strong and also during low-force but fatiguing unilateral muscle contractions (70, 71, 115). Therefore, the magnitude of the load or fatigue during the RT set could affect the magnitude of CE through the level of ipsilateral hemisphere activation (111). This prediction is supported by the observation that, for example, eccentric compared with other types of

muscle contraction is associated with heightened activation of the ipsilateral hemisphere (112), resulting in greater CE of voluntary force (108).

However, most studies examining RT-induced CE used training loads >50% of MVIC or 1RM (39, 63, 74, 89, 325, 327) and the few studies using low-load RT reported inconsistent results (59, 340), as low-load RT for 3-4 weeks with or without blood flow restriction produced 26% (59) or no CE (340), 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 (5x6 with a 10 repetition maximum load) compared with a cluster training set configuration (30 repetitions with 18.5 s of rest between each rep) (342), 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 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 (i.e. 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 transcranial magnetic stimulation (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.

8.3 MATERIAL AND METHODS

8.3.1 Participants

Healthy, recreationally active men (n=42, 21.8±2.4y, 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 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 university Institutional Review Board. 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 48h 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.

8.3.2 Study design and training

Fig. 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 four weeks of RT, participants came to the laboratory for the final post-test (POST, 96-120h after last training session). Each testing session started with maximal voluntary isometric contractions (MVIC), followed 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±4.3y), low-load RT to concentric muscular failure (LLF, n=11, 20.8±1.3y), high-load RT to concentric muscular failure (HLF, n=11, 21.4±1.4 y), and high-load RT without failure (HLNF, n=11, 21.8±1.5 y). CON continued with their daily habits during four weeks between PRE-2 and POST. The training groups performed unilateral knee extension RT with the dominant

leg (self-reported) four times per week for four weeks (Monday, Tuesday, Thursday, Friday). We choose a high frequency RT (4d/wk) 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 (339).

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 (i.e., 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 four 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 two 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 (429). 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.

8.3.3 Set-up

Participants sat in a custom made chair with the hip, knee and ankle at 90º, and the torso restrained with belts to avoid displacement (Fig. 1A). Both legs were fastened with two rigid straps around the ankle to two force transducers (NL63, 200kg; Digitimer, Welwyn Garden City, UK) to measure voluntary force (band-pass-filtered 5-2,500Hz, amplified x1,000 and sampled at 2kHz).

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 (x600-1000 depending on the baseline M_{max} amplitude at PRE-1), bandpass filtered (10-500Hz), 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, Cambridge, UK) for further analysis.

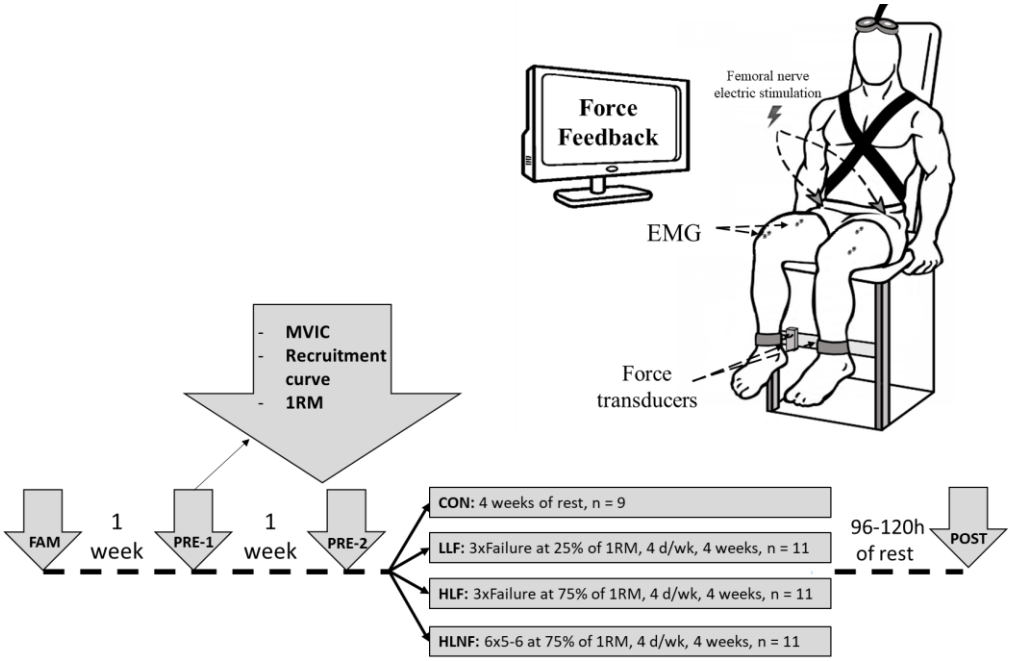

Figure 11. Schematic view of the set-up and protocol. (A) Subjects sat in a custom made chair with the hip, knee and ankle at 90º and the torso restrained with belts to avoid displacement during isometric contrations. (B) Schematic representation of the experimental design.

8.3.4 Maximal voluntary force tests

At the beginning of the testing sessions, in the position described above (Fig. 1A), participants performed two unilateral three-to-five 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 EMGRMS of the VL (VL-EMGRMSmax) and the RF (RF-EMGRMSmax) was computed offline in a time window of 500ms around the peak force and normalized to the amplitude of the Mmax.

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, Cesena, Italy). 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 90º to 180º 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.

8.3.5 Transcranial magnetic stimulation

Single-pulse TMS was delivered to the left and right motor cortices (M1) using a concave double-cone coil (120 mm) which induced a posterior-anterior intracranial current connected to a DuoMag (Rogue Resolutions Ltd, Cardiff, UK)

magnetic stimulator. The optimal stimulation point of each leg was obtained by exploring the estimated centre of the quadriceps muscles cortical representation. The point at which motor evoked potentials (MEP) were the largest in each session was marked on the scalp with a permanent marker.

To measure CSE a recruitment curve (RC) was measured in both legs during a unilateral contraction of a 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 150ms previous to the pulse was also measured and averaged for each session.

8.3.6 Peripheral nerve stimulation

The maximal compound muscle action potential (M_{max}) of both legs was obtained via single-pulse electrical stimulation (200μs 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} was measured and averaged. The average M_{max} value of each testing session was then used for normalization procedures of all the other EMG variables.

8.3.7 Statistics

The normality and homogeneity of variables was tested with Kolmogorov-Smirnov 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 were performed for all variables. When no significant differences were found between PRE-1 and PRE-2, the mean value was used for subsequent analysis (PRE). A one-way ANOVA with group (LLF, HLF, HLNF) as factor was performed for the training variables (REPs/d, VOL/d and RPE/d). A three-way 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 and VL and RF M_{max}. When significant interactions or main effects were found, Bonferroni correction was applied to account for multiple comparisons in the post-hoc analyses. ES are presented as partial eta-squared values (η_p^2; small: 0.01; medium: 0.06; large: 0.14) for the factors of the RM-ANOVAs and as Cohen's d for the paired comparisons. 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, Chicago, IL) was used for statistical analysis. Statistical significance was set at $P \leq 0.05$.

8.4 RESULTS

8.4.1 Reliability

Intersession reliability ranged from 0.65 to 0.96 for all variables (See Table 5).

Table 5. PRE-1 and PRE-2 mean raw values, absolute and relative changes from PRE-1 to PRE-2, paired T-test P value, Cohen's d effect size and inter-session reliability for all variables (n = 42).

	PRE-1	PRE-2	Δ, abs	Δ, %	T-Test , P value	d	Inter-Session ICC (95% CI)
Trained:							
1RM (kg)	57.12 ± 11.15	57.93 ± 10.35	0.81	1.40	0.08	0.07	0.96 (0.93, 0.98)
MVIC (N)	595.29 ± 95.91	603.08 ± 97.62	7.80	1.31	0.11	0.08	0.94 (0.89, 0.97)
VL-EMG$_{RMS}$ (%M$_{max}$)	0.087 ± 0.033	0.088 ± 0.035	0.002	1.84	0.56	0.03	0.87 (0.77, 0.93)
RF-EMG$_{RMS}$ (%M$_{max}$)	0.107 ± 0.043	0.109 ± 0.044	0.002	2.12	0.35	0.05	0.94 (0.89, 0.97)
VL-AURC (a.u)	96.09 ± 56.79	95.34 ± 59.36	-0.75	-0.78	0.82	0.01	0.93 (0.88, 0.96)
RF-AURC (a.u)	164.42 ± 96.31	160.54 ± 94.88	-3.89	-2.36	0.61	0.04	0.87 (0.77, 0.93)
VL-M$_{max}$ (mV)	4.99 ± 1.54	4.91 ± 1.52	-0.08	-1.65	0.54	0.05	0.84 (0.72, 0.91)
RF-M$_{max}$ (mV)	3.80 ± 1.40	3.82 ± 1.43	0.02	0.56	0.84	0.01	0.89 (0.80, 0.94)
Untrained:							
1RM (Kg)	58.90 ± 10.43	59.48 ± 10.19	0.57	0.97	0.23	0.06	0.96 (0.92, 0.98)
MVIC (N)	592.72 ± 101.18	597.03 ± 100.38	4.31	0.72	0.38	0.02	0.95 (0.91, 0.97)
VL-EMG$_{RMS}$ (%M$_{max}$)	0.078 ± 0.030	0.080 ± 0.031	0.002	2.40	0.64	0.06	0.65 (0.43, 0.79)
RF-EMG$_{RMS}$ (%M$_{max}$)	0.108 ± 0.047	0.107 ± 0.038	-0.001	-0.88	0.83	0.02	0.79 (0.64, 0.88)
VL-AURC (a.u)	96.47 ± 49.67	104.73 ± 52.00	8.25	8.55	0.057	0.16	0.84 (0.72, 0.91)
RF-AURC (a.u)	158.96 ± 70.35	163.07 ± 71.28	4.11	2.59	0.57	0.06	0.78 (0.63, 0.88)
VL-M$_{max}$ (mV)	5.18 ± 1.92	5.12 ± 1.91	-0.07	-1.32	0.60	0.03	0.88 (0.78, 0.93)
RF-M$_{max}$ (mV)	3.31 ± 1.14	3.37 ± 1.05	0.05	1.50	0.62	0.05	0.83 (0.70, 0.90)

d: Cohen's d effect size; ICC: Intraclass correlation coefficient; CI: Confident interval; 1RM: one repetition maximum; MVIC: maximum voluntary isometric contraction; VL: vastus lateralis; EMG$_{RMS}$: maximum electromyography root mean square; RF: rectus femoris; MEP: Motor evoked potential; AURC: area under the curve; M$_{max}$: Maximal compound muscle action potential.

8.4.2 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=0.001) and HLNF (33±0.8 reps/day, d=7.0, P=0.001) without differences between the HLF and HLNF (d=0.1, P=0.99). However, the total volume was not different between LLF (1877±533 Kg/d), and HLF (1504±335 Kg/d, d=0.84, P=0.112), and HLNF (1470±297 Kg/d, d=0.94, P=0.072) or between HLF and HLNF (d=0.1, P=0.99). 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=0.001).

8.4.3 Voluntary dynamic force (1RM)

Before training, 1RM values were similar between groups in each leg (all P>0.05). After four weeks of RT, 1RM of the trained leg increased in HLF (20%, d=0.70, P=0.001) and HLNF (15%, d=0.61, P=0.001) but not in LLF (2%, d=0.09, P=0.59) or CON (2%, d=0.01, P=0.73). 1RM of the untrained leg also increased in the groups that trained with high load (HLF: 5 %, d=0.27, P=0.001; HLNF: 6 %, d=0.26, P=0.009) but not in LLF (0.6%, d=0.01, P=0.74) or CON (0.2%, d=0.01, P=0.93) (Fig. 12, see Table 6 and 7 for raw values, main effects and interactions). The increase in 1RM of the trained and untrained leg correlated r=0.34 (P=0.028).

Table 6. 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)							
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
RF-EMG$_{RMS}$ (%M$_{max}$)				**RF-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
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
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

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

Table 7. RM-ANOVA main effects and interactions.

	Leg	Leg*Group	Time	Time*Group	Leg*Time	Leg*Time*Group
1RM (kg)	F (1, 38) = 0.14; P = 0.91; η_p^2 = 0.01	F (3, 38) = 1.41; P = 0.25; η_p^2 = 0.10	F (1, 38) = 29.00; P = 0.001; η_p^2 = 0.43	F (3, 38) = 6.85; P = 0.001; η_p^2 = 0.35	F (1, 38) = 9.61; P = 0.004; η_p^2 = 0.20	F (3, 38) = 2.54; P = 0.07; η_p^2 = 0.17
MVIC (N)	F (1, 38) = 2.04; P = 0.16; η_p^2 = 0.05	F (3, 38) = 2.47; P = 0.08; η_p^2 = 0.16	F (1, 38) = 12.68; P = 0.001; η_p^2 = 0.25	F (3, 38) = 6.98; P = 0.001; η_p^2 = 0.36	F (1, 38) = 8.50; P = 0.006; η_p^2 = 0.18	F (3, 38) = 6.86; P = 0.001; η_p^2 = 0.35
VL-EMG$_{RMS}$ (%M$_{max}$)	F (1, 38) = 6.07; P = 0.02; η_p^2 = 0.14	F (3, 38) = 0.70; P = 0.56; η_p^2 = 0.05	F (1, 38) = 0.10; P = 0.75; η_p^2 = 0.01	F (3, 38) = 0.60; P = 0.62; η_p^2 = 0.05	F (1, 38) = 0.74; P = 0.39; η_p^2 = 0.02	F (3, 38) = 0.79; P = 0.51; η_p^2 = 0.06
RF-EMG$_{RMS}$ (%M$_{max}$)	F (1, 38) = 2.70; P = 0.11; η_p^2 = 0.07	F (3, 38) = 3.22; P = 0.03; η_p^2 = 0.20	F (1, 38) = 1.53; P = 0.22; η_p^2 = 0.04	F (3, 38) = 0.09; P = 0.96; η_p^2 = 0.01	F (1, 38) = 16.13; P = 0.001; η_p^2 = 0.30	F (3, 38) = 0.14; P = 0.94; η_p^2 = 0.01
VL-AURC (a.u)	F (1, 38) = 0.99; P = 0.32; η_p^2 = 0.03	F (3, 38) = 1.25; P = 0.31; η_p^2 = 0.09	F (1, 38) = 3.40; P = 0.07; η_p^2 = 0.08	F (3, 38) = 3.07; P = 0.039; η_p^2 = 0.19	F (1, 38) = 0.19; P = 0.66; η_p^2 = 0.01	F (3, 38) = 0.28; P = 0.83; η_p^2 = 0.02
RF-AURC (a.u)	F (1, 38) = 0.19; P = 0.67; η_p^2 = 0.03	F (3, 38) = 3.83; P = 0.02; η_p^2 = 0.23	F (1, 38) = 3.81; P = 0.06; η_p^2 = 0.09	F (3, 38) = 0.94; P = 0.43; η_p^2 = 0.07	F (1, 38) = 1.23; P = 0.27; η_p^2 = 0.03	F (3, 38) = 0.46; P = 0.71; η_p^2 = 0.03
VL-M$_{max}$ (mV)	F (1, 38) = 0.05; P = 0.83; η_p^2 = 0.01	F (3, 38) = 0.97; P = 0.41; η_p^2 = 0.07	F (1, 38) = 0.22; P = 0.64; η_p^2 = 0.01	F (3, 38) = 0.68; P = 0.57; η_p^2 = 0.05	F (1, 38) = 0.42; P = 0.52; η_p^2 = 0.01	F (3, 38) = 0.36; P = 0.79; η_p^2 = 0.03
RF-M$_{max}$ (mV)	F (1, 38) = 3.55; P = 0.07; η_p^2 = 0.08	F (3, 38) = 1.46; P = 0.24; η_p^2 = 0.10	F (1, 38) = 1.13; P = 0.29; η_p^2 = 0.03	F (3, 38) = 2.30; P = 0.09; η_p^2 = 0.15	F (1, 38) = 2.34; P = 0.13; η_p^2 = 0.06	F (3, 38) = 1.70; P = 0.18; η_p^2 = 0.12

1RM: one repetition maximum; MVIC: maximum voluntary isometric contraction; VL: vastus lateralis; EMG$_{RMS}$: maximum electromyography root mean square; RF: rectus femoris; MEP: Motor evoked potential; AURC: area under the curve; M$_{max}$: Maximal compound muscle action potential.

8.4.4 Voluntary isometric force and EMG

Before training, MVIC force and VL and RF-EMG$_{RMS}$ were similar between groups for both legs (all P>0.05). MVIC force increased in the trained leg in HLF (6%, d=0.35, P=0.001) and HLNF (12 %, d=0.67, P=0.001) but not in LLF (-3%, d=0.14, P=0.12) or CON (1%, d=0.08, P=0.58). No changes occurred in the untrained leg MVIC force (CON: 0.6%, d=0.35, P=0.74; LL: 0.2%, d=0.35, P=0.90; HLF: 0.3%, d=0.35, P=0.85; HLNF: 4%, d=0.35, P=0.053) (Fig. 12, Table 6 and 7). The increase in MVIC force of the trained leg correlated with the increase in the trained leg 1RM (r=0.42, P=0.006) and the changes in untrained leg MVIC force (r=0.46, P=0.002).

VL-EMGRMS did not change in either leg. The RF-EMGRMS increased from baseline in the trained leg of all groups (13%, d=0.33, P=0.005) (Table 6 and 7). The changes in RF-EMGRMS correlated with those obtained in the trained leg MVIC force (r=0.31, P=0.049).

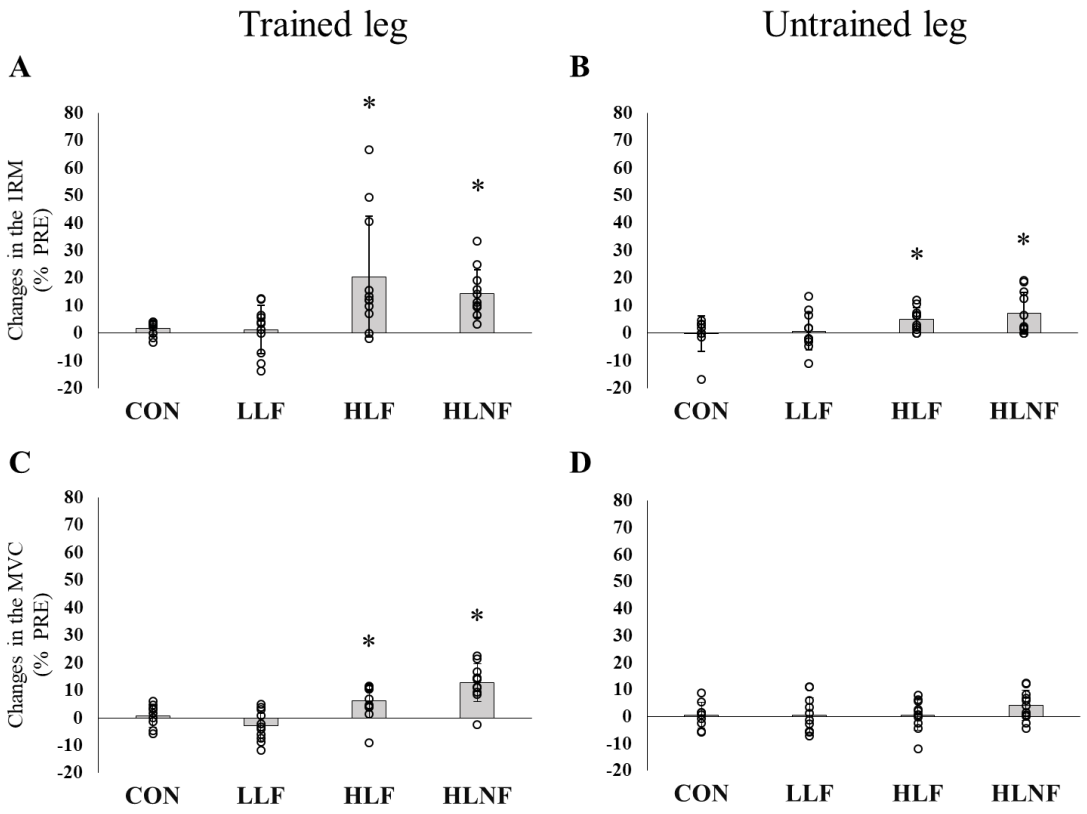

Figure 12. Trained (left column) and untrained (right column) mean and individual changes in 1RM (upper row) and MVC (lower row). (*) shows a statistically significant difference (P < .05) to PRE values.

8.4.5 Corticoespinal excitability

Before training, AURC-VL, AURC-RF were similar between groups in both legs (all P>0.05). Four weeks of RT reduced the AURC-VL in both legs in HLNF (-19%, d=0.44, P=0.011) but not in CON (17%, d=0.27, P=0.13), LLF (-14%, d=0.23, P=0.12) or HLF (-10%, d=0.20, P=0.22) (Figure 13, Table 6 and 7). No changes

occurred in the AURC-RF (Figure 14, Table 6 and 7). Changes in CSE in the VL or the RF were not related to changes in 1RM (r=-0.10 and r=-0.11, respectively, all P>0.05) or MVIC (r=-0.03 and r=-0.06, respectively, all P>0.05).

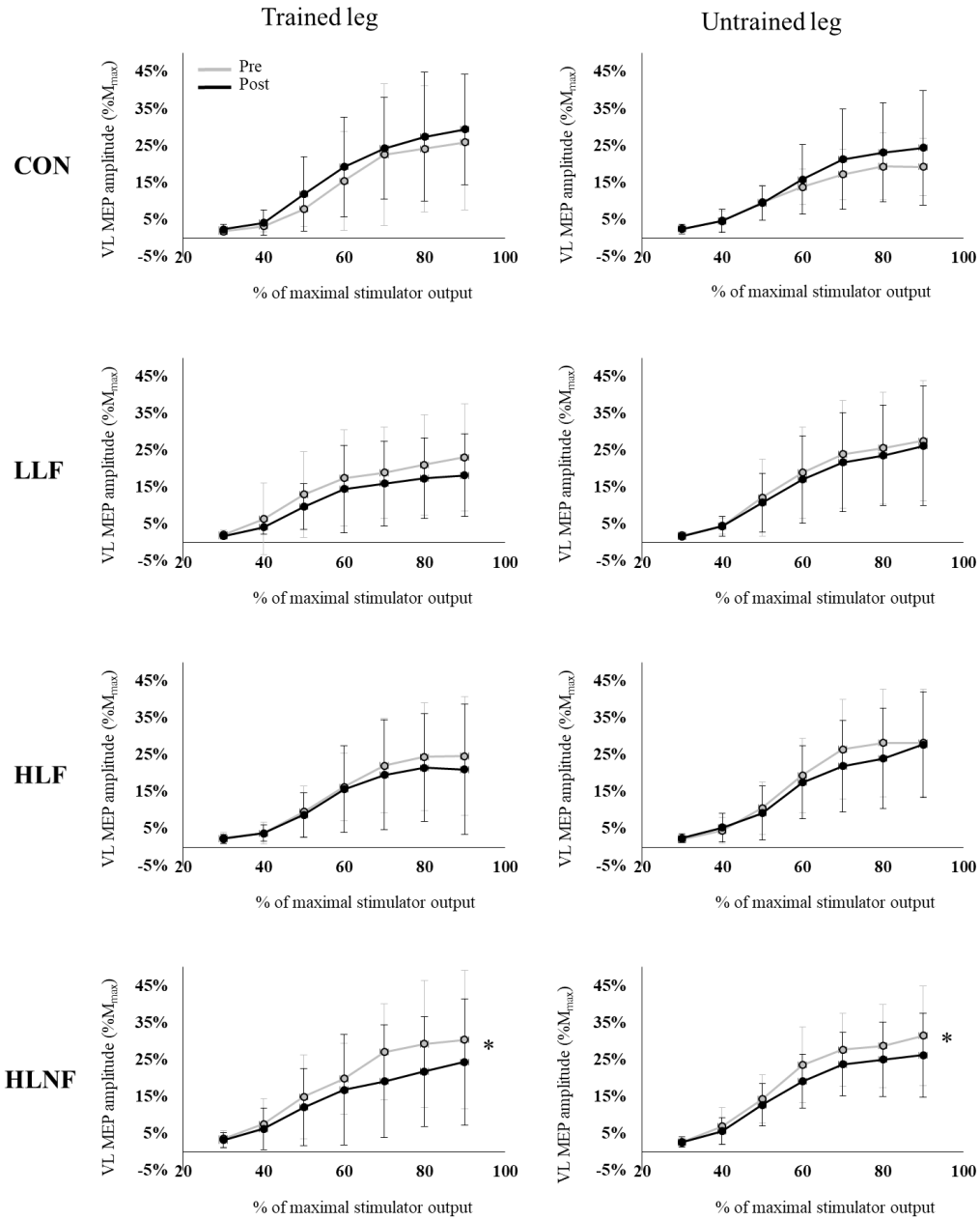

Figure 13. Trained (left column) and untrained (right column) leg vastus lateralis recruitment curve of each group. (*) shows a statistically significant (P < .05) difference between PRE to POST in the area under the recruitment curve.

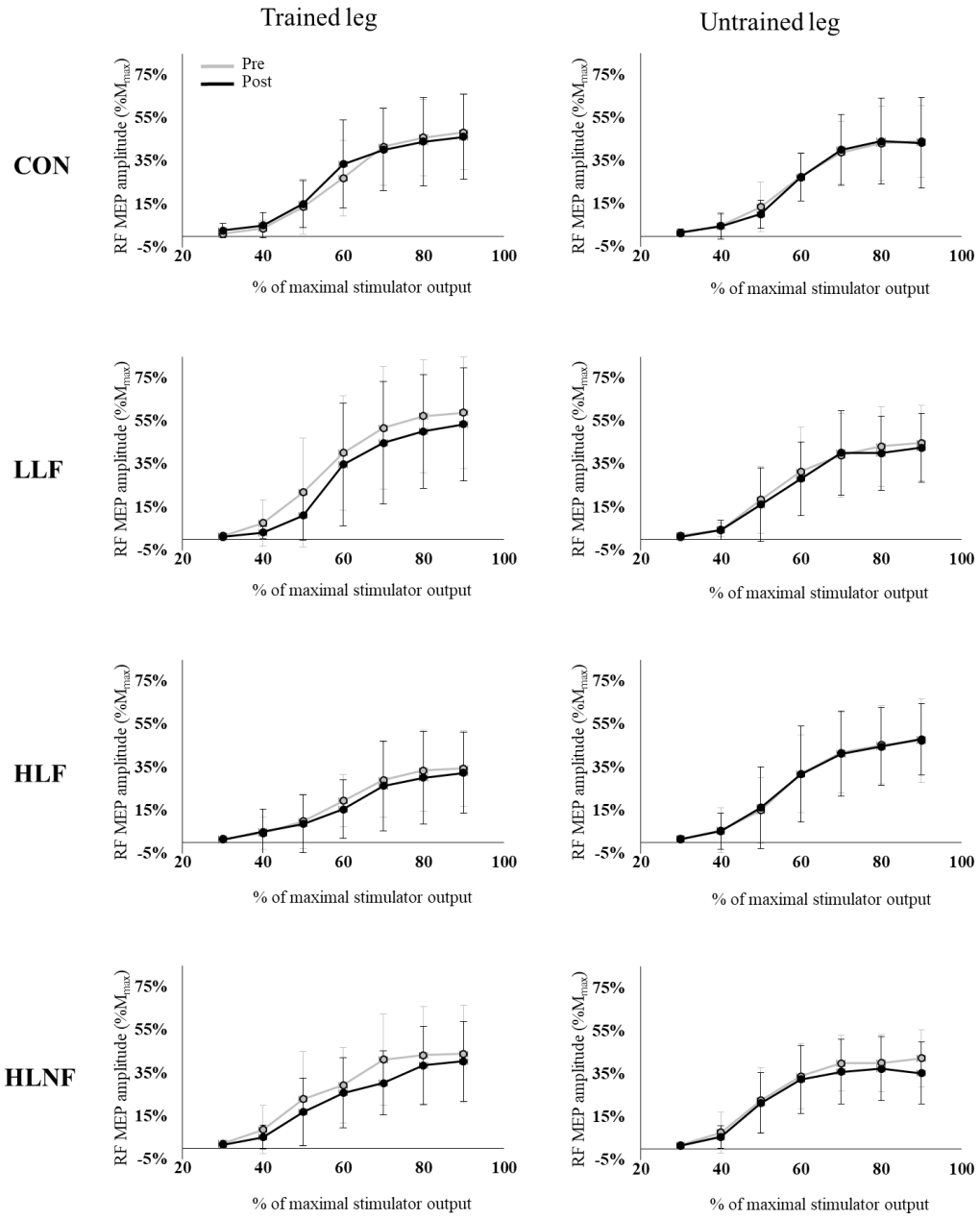

Figure 14. Trained (left column) and untrained (right column) leg rectus femoris recruitment curve of each group.

8.4.6 Responses to peripheral nerve stimulation

Before training, VL or RF M_{max} were similar between groups in both legs (all $P>0.05$). M_{max} did not change in any muscle, leg or group (Table 6 and 7).

8.5 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 (96). 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 (96). 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 (97), Therefore, this suggests that when low-loads are used during RT, increases in maximal voluntary force may occur more slowly and longer training periods may be needed compared with high-load RT, which could explain a lack of changes after 4 weeks in the present study. Furthermore, the high frequency (4d/wk) 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. The combination of training to failure, which is associated with high levels of muscle damage (430), and the high frequency of training allowing a shorter time for recovery between training bouts, could have had a cumulative effect that may have led to greater levels of muscle damage affecting the force-generating capacity even after 96-120h 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 (63). 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 (67). The intensity of the muscle contraction is a strong modulator of the ipsilateral hemisphere activation, with strong contractions leading to greater ipsilateral hemisphere activation (70, 115) and intensity-dependent reductions in intracortical inhibition and interhemispheric inhibition from the contralateral to the ipsilateral hemisphere (115). Therefore, RT load may influence the magnitude of CE (111) 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 (59, 340), 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 (340). There is a correlation between force improvements in the trained and untrained limb in previous studies (39, 325), which is also present in the current results (r=0.34 and r=0.46 for 1RM and MVIC force, respectively). From this correlation 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 has low effectiveness in producing CE. This could be due to low activation of the ipsilateral hemisphere during unilateral low-load contractions, producing a sub-threshold stimulus for CE (420, 431).

Muscle fatigue during the set could also enhance RT adaptations in the trained limb (432) by increasing metabolic stress and motor unit activation (235). 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, four 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.(103) However, as discussed above, the high frequency of training used in our training protocol plus leading sets to muscular failure could have had a cumulative effect leading to an overtraining

that may have hindered any advantages of training to failure in the trained leg. 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 unilateral contractions can also increase the level of activation of the ipsilateral hemisphere (71). Thus, we hypothesized that RT to failure would increase the stimulus to the untrained hemisphere, increasing the magnitude of CE. Most CE studies used training protocols leading the sets to or close to muscle failure (39, 74, 89, 327, 337). Only one study compared the effects of two training programs associated with different levels of fatigue during the training session on CE (342). 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 influence the magnitude of CE (342). However, our results show that reaching muscle failure in each set did not further increase CE. Differences in the training protocols between studies could explain the discrepant data. The low-fatigue protocol (342) consisted of 30 repetitions performed continuously with 18.5 s of rest between repetitions, which has been associated whit low levels of fatigue and the maintenance of the power level during the whole training session (343). However, the high-fatigue protocol (342) (5x6, 10RM) was very similar to our HLNF protocol (6 sets x 5-6 reps, 75% of 1RM). Therefore, the high-fatigue protocol in our study (i.e., HLF), reaching muscle failure in each set, represents the protocol leading to the greater amount of fatigue. Taken together, these observations suggest that a minimum threshold of fatigue is needed to maximize CE with high-load RT (342), but levels of fatigue above this threshold do not further enhance 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 (42). These results suggest that sensitivity of CE to fatigue in the trained limb may depend on the trained segment, being greater in muscles of the upper limbs.

It is believed that neural adaptations underlie the increases in maximal voluntary force after RT (67). Increases in CSE may lead to a better efficacy of the motor command through a greater neural drive from corticospinal neurons to the motoneurons. Recent meta-analysis suggest that RT increase CSE in the trained limb when measured during contraction (62), but do not change in the untrained limb (63). 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 (39, 327, 433) or even decreases (31) 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 (63). Furthermore, our results show that changes in CSE after 4 weeks of RT are not related to changes in maximal dynamic or isometric voluntary force. 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 (74) and none in the trained limb. Other study reported a correlation between CSE in the untrained limb measured during contraction of the trained limb and CE (325). 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 (325). 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 absence of correlation between CSE and performance in ballistic contractions (412) 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 (433), like the reticulospinal tract (434, 435), which could not be detected by TMS of the motor cortex.

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 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.

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IX – SUMMARY AND GENERAL DISCUSSION

IX – SUMMARY AND GENERAL DISCUSSION

The present thesis aimed to determine the effects of the modification of training load and fatigue during unilateral RT on the CE of voluntary force that occurs with unilateral RT. For that purpose, we focused on the effect of those variables on two levels. In the first level we focused on the effect of training load on the acute neural changes occurring after a single session of unilateral RT. Those acute neural changes have been suggested to be the trigger for long-term adaptations occurring after short RT periods in both, the trained and untrained side (75, 77, 118). Therefore, knowing how training load affects those acute neural changes could inform about the potential of different training loads to produce long-term neural and functional adaptations. The second level was the actual effect of training load and fatigue during unilateral RT on chronic neural and functional adaptations in the trained and the untrained side.

For that purpose, we performed four studies whose results show that 1) the responses to transcranial but not corticospinal tract stimulation after a single session of RT are load-dependent in the trained side (420); 2) training variables like the type of contraction, load, fatigue, and strategies of pacing the movement may affect the acute and chronic adaptations in the untrained hemisphere contributing to inconsistencies found in the literature (111); 3) an acute bout of RT leads to load-dependent increases in corticospinal but not intracortical excitability in the trained but not the untrained side (431); 4) training load but not the degree of fatigue influences voluntary force increases in the trained and untrained side after four weeks of unilateral RT (436).

Based on a previous model that found an acute increase in CSE after a single session of isometric unilateral RT (77), we performed an initial study to determine the effects of RT load on the acute responses to TMS and corticospinal tract stimulation in the trained side. Results show that the training load of an acute bout of isometric unilateral RT affects CSE measured by TMS but does not affect the responses to corticospinal tract stimulation (420). Furthermore, results show that training load not only affected the magnitude of the increases in BB

CSE but also the duration of the effect. The disparate effects of load on TMS and cervicomedullary responses suggest that load-dependent changes occur at cortical or corticospinal level but not at the α-motoneuron level (420). It is likely that the increase in CSE is related to use-dependent corticomotor plasticity mediated by LTP-like mechanisms (385, 386, 420).

The results from the complementary experiment suggest that exercise volume also affects the acute responses measured with TMS after a single session of unilateral RT (420). Therefore, the results from the first study show that the manipulation of the training load or volume impacts the acute responses to a single bout of RT in the trained side. Although it is still unknown if this dose-response relationship between the training load and acute corticospinal changes lead to similar dose-response adaptations after chronic periods of RT, the present results could explain why high-load RT is more effective than low-load RT eliciting the neural adaptations underlying the increases in maximal voluntary force (97).

Because the main focus of the present thesis was on the neuromuscular acute changes and adaptations in the untrained side, the next step was to detect the training variables with a greater potential influence on the acute changes and chronic neural adaptations underlying CE whose effect has not been systematically investigated. Thus, the aim of the systematic review was to determine the effects of training variables on the acute responses and chronic adaptations measured with TMS in the untrained hemisphere after unilateral RT (111). Independently of the training variables, the present systematic review found no clear results regarding the effects of a single session of RT on the untrained hemisphere CSE, intracortical inhibition or IHI (111). However, although not consistently, results from the chronic studies show an increase in CSE (n = 8 studies), a reduction in intracortical (i.e. SICI, n = 5 studies) and corticospinal inhibition (i.e. SP, n = 5 studies) in the untrained hemisphere, and reduced IHI from the trained to the untrained side (n = 1 study), supporting the neural origin of CE (63, 64, 66, 67, 69, 111).

Although inconsistency in the results could be related to differences in the methodology used to measure neural adaptations, it also seems to be related to the training protocol used in each study (111). The systematic review revealed that most of the acute and chronic studies that found increased CSE, and/or

reduced intracortical (i.e. SICI) or corticospinal inhibition (i.e. SP), included dynamic RT combining eccentric and concentric contractions (39, 89, 90, 109, 111, 327, 335-337). Eccentric contractions are associated with greater neural resources needed for programming and planning the movement compared to static or concentric contractions (172), leading to a greater concurrent activation of the untrained hemisphere (112, 113). Therefore, it is likely that this greater concurrent activation of the untrained hemisphere serves as a greater training stimulus, thus explaining the greater neural and functional adaptations in the untrained limb after eccentric unilateral RT (108, 109). The review also shows that externally pacing dynamic RT with an external auditory cue could enhance acute responses (76) and chronic neural adaptations (74, 90, 335-337) in the untrained hemisphere. These greater adaptations with external auditory cues could be related to the synchronized arrival of afferent inputs from the auditory cortex with the activation of the corticospinal cells in the M1, leading to an enhancement of synaptic efficacy due to Hebbian principles (418).

However, the present review highlights the lack of direct evidence about the effect of critical variables such as load or fatigue on the acute responses and chronic adaptations in the untrained hemisphere (111). The amount of concurrent activation of the untrained hemisphere increases with the muscle contraction intensity (114, 193), leading to parametric increases in CSE and reductions in SICI and IHI from the active to the resting hemisphere (70, 115, 181, 198-200). Similarly, high levels of fatigue in the active limb lead to a higher activation of the ipsilateral hemisphere (71). Therefore, greater adaptations in the untrained hemisphere could be expected with high-load contractions and greater levels of fatigue in the contracting limb during unilateral RT. However, the present review could not compare the effect of RT load on the acute and chronic neural adaptations of the untrained hemisphere because all the studies used training loads > 70% of the maximum force in the trained movement (111). Regarding fatigue, one study found results contrary to our hypothesis, showing a decrease in ipsilateral CSE after a set of low-load RT until failure (405). However, no other acute or chronic study (at the time of submission) had addressed the effects of fatigue during unilateral RT on the responses and adaptations of the untrained hemisphere or CE. Therefore, in the subsequent studies we focused on the effects of different training loads (low vs high) and the level of fatigue during unilateral

RT on the CE and their associated neural mechanisms. A detailed understanding of the effect of the manipulation of those variables on the acute changes and adaptations on the untrained limb, could help to optimize exercise prescription and maximize the benefits of unilateral RT.

Therefore, in the third study we determined the effect of training load during a single unilateral RT session on acute changes in CSE, and its relation with changes in intracortical inhibitory and facilitatory circuits in the trained and the untrained hemisphere (431). As with the trained side (75, 77, 118, 420), acute changes in the untrained corticospinal tract could be the trigger for the sustained adaptations leading to increases in maximal force of the untrained limb (111). Therefore, in this study we replicated the RT model used in the first study (420) with two purposes. First, to further delimit the origin of the load-dependent increases in CSE found in the trained hemisphere in the first study (420). The increase in the response to single pulse TMS (420) could be related to changes in intracortical circuits that influence the indirect activation of the corticospinal neurons and could be tested with paired pulse TMS. Second, to determine if the concurrent activation of the untrained hemisphere during unilateral contractions leads to similar load-dependent acute changes in the untrained corticospinal tract, which could inform on the potential effect of training load on CE. Despite the systematic review detected a lack of knowledge about the role of load and fatigue during RT on the adaptations in the untrained limb, we did not include fatigue as a variable in the present study. The main reason was that we wanted to replicate in the untrained BB the model that showed a load-dependent effect on CSE in the trained BB (420).

In line with the first study, the results showed that high- but not low-load RT increased CSE in the trained BB. Changes in α-motoneuron excitability or in the efficacy of the corticospinal-motoneuronal synapse are unlikely to underlie the load-dependent increases in CSE (420). This is supported by the first study of this thesis showing no load-dependent increases in CMEPs (420), and by previous studies showing that increases in CMEPs after a single session of RT do not always occur (257). However, contrary to the hypothesis, the results of the present study show that a single session of isometric RT does not reduce the efficacy of GABA-A (measured with SICI) and GABA-B (measured with SP) receptor-mediated inhibitory intracortical circuits projecting to cortical excitatory

neurons. Intracortical circuits leading to SICI or ICF affect mainly the size of the late I-waves that compose the MEP (134). Therefore, the change in the MEP amplitude without changes in SICI or ICF may be related to an increase in the efficacy of the monosynaptic conections responsible of the early I-waves, which are not affected by SICI or ICF (437). Indeed, a recent study showed that the excitability of supragranular layer neurons that lead to the early I-waves is sensitive to the level of torque generated by a muscle contraction, probably because the afferent feedback coming from muscle is integrated at this level (438). Therefore it could be the case that high-load RT leads to greater afferent input during training, leading to a greater input from the supragranular layer neurons to corticospinal neurons, which may lead to a transient increase in the synaptic efficiency. Consequently this would increase the output from the α-motoneurons to the trained BB, leading to greater MEP amplitudes despite the same stimulation intensity and without affecting SICI or ICF (437, 438)

Regarding the untrained BB, we hypothesized that the concurrent activation during unilateral RT would also lead to an increase in CSE (431). Specifically, based on the load-dependent increase found in the trained BB in the first study (420), we thought that the lower concurrent activation in the untrained hemisphere, representing a lower training stimulus, would increase CSE in the untrained BB to a lower magnitude compared to the trained BB and only after high-load RT. However, the results show that contrary to what happens in the trained BB, a single session of isometric unilateral RT does not affect CSE or the efficacy of intracortical circuits regardless of RT load (431). This lack of change adds to the inconsistencies found in the systematic review regarding the effect of just one session of unilateral RT on the corticospinal and intracortical responses of the untrained hemisphere (111).

The lack of change in CSE could be related to the magnitude of the concurrent activation of the untrained hemisphere not reaching a critical threshold to produce lasting changes. The combined results from the first and the present study suggest that, in the trained hemisphere, this threshold of activation is somewhere between the activation produced by a contraction of 25% (not producing changes) and 50% (increasing CSE) of the MVC (420, 431). Therefore, it seems that unilateral isometric progressive contractions of 75% of MVC does not lead to an enough concurrent activation of the untrained hemisphere to surpass

this threshold. In fact, when no feedback about the untrained limb is given to the subjects, a unilateral MVC leads to inadvertent activation of the untrained homologous muscle (208). This inadvertent activation in the untrained BB produces a EMG amplitude equivalent to the level of EMG present during a voluntary contraction of a 17 ± 14% of the MVC of the untrained BB (208). This suggests that the concurrent activation of the untrained hemisphere during progressive isometric unilateral contractions is likely well below the activation threshold (between 25-50% of MVC in the trained BB) needed to produce changes.

Discrepancies with other studies that found increases in the response to TMS in the untrained hemisphere could be related to the influence of other training variables like the type of muscle contraction (76, 111). The inclusion of dynamic contractions could have had an additive effect with the high-load used in those studies, increasing the activation of the untrained hemisphere compared to the progressive isometric contractions of the present study (111-113). However, chronic unilateral RT using isometric contractions also led to long-term neural and functional adaptations in the untrained limb in previous studies (325). Therefore, it seems that it is not possible to infer the long-term effectiveness of a RT protocol to produce neural and functional adaptations in the untrained limb based just on one session of unilateral RT.

Following the last conclusion, we therefore focused the fourth study on the long-term effects of training load (75% vs 25% of 1RM) and the level of fatigue during the set (reaching failure or not), on neuromuscular adaptations of the trained and untrained leg extensors (436). The effect of both variables has been extensively studied in the trained side (96, 103, 107). However, despite the greater activation of the untrained hemisphere during high intensity contractions (114, 193) and high degrees of fatigue (71), and therefore the potential to influence the untrained limb adaptations, evidence about the effect of manipulating this training variables on CE is scarce. In partial agreement with the hypothesis, the results of the last study of the present thesis showed that increases in maximal force in the untrained and trained leg occur only with high-load unilateral RT and are not affected by the magnitude of fatigue during training (i.e.: sets leading or not to muscle failure). Results also show that those increases in force are unrelated to changes in CSE in both legs (436).

The lack of increases in maximal force of the trained limb after low-load RT, could be related to high levels of muscle damage derived from the combined effect of training to failure (430) and the high training frequency (4d/wk.) used in the present study (436). However, the present results in the trained leg are in accordance with previous studies suggesting a lower effectiveness of low-load RT versus high load RT (96, 97), and add new information regarding the effect of load on CE and associated neural adaptations. Overall, the present results suggest that high-load RT is required to maximize the increases in maximal voluntary force in the trained and the untrained limb. Thus, low-load RT is not suitable to be used on unilateral RT models aiming to increase the force of the untrained limb, probably because of a low concurrent activation of the untrained hemisphere during low intensity unilateral contractions (70, 115). However, it could be the case that, as occurs in the trained side (97), low-load RT requires more time and training sessions to increase maximal voluntary force in the untrained limb. Therefore, the present results and the correlations between the force improvements in the trained and the untrained side (18), suggest that the magnitude of CE may depend on the effectiveness of the training protocol to produce increases in maximal voluntary force of the trained limb. This would explain why high-loads and eccentric contractions lead to greater increases in maximal force in the trained (268), and as a consequence, in the untrained side (108, 109).

Regarding fatigue, our results in the trained limb agree with previous results suggesting that muscle failure is not a necessary stimulus to maximize the increases in maximal voluntary force (103, 104, 106). However, due to the increased untrained hemisphere activation that occurs with higher levels of fatigue (71), we hypothesized that this variable could have some benefit in the untrained limb. Notwithstanding, in contrast with a previous study looking at the effect of fatigue during the set on CE (342), our results do not support this hypothesis. However, this discrepancy could be related to the different level of fatigue achieved in the training protocols of both studies (low-fatigue vs medium fatigue (342), and medium fatigue vs high fatigue (failure) (436). Therefore, the combined results of both studies suggest that a minimum threshold of fatigue may be needed to maximize CE with high-load RT, but greater levels of fatigue

(reaching or close to muscle failure) do not have further benefits on the untrained limb.

Finally, regarding neural adaptations, contrary to our hypothesis we found a decrease in the CSE in the VL of the HLNF group, without any change in the CSE of the RF in any group. It has been proposed that increases in CSE after RT would increase the neural drive to the α-motoneurons and ultimately muscle force (62, 422, 439). However, the lack of change (HLF) and the decrease (HLNF) in CSE do not support the role of an increase in CSE as a mechanism to enhance the force in either leg. Furthermore, there was no correlation between changes in CSE and maximal voluntary force in any leg, in accordance with most of the studies that did not report correlation between changes in force and CSE or even between other behavioural outcomes and CSE (30-42, 44, 45, 62, 74, 327, 332, 335, 377, 440, 441). This may suggest that CSE is not an optimal measurement to prove functional adaptations in the neuromuscular system. Because large increases in muscle mass are unlikely after just four weeks of RT, increases in maximal voluntary force may be related to other neural adaptations not probed with single pulse TMS, such as decreased intracortical inhibition (376), decreased antagonist co-activation (355, 356), or adaptations in other descending tracts or supraspinal structures with a role in force generation that can not be tested with TMS (433-435).

To sum up, the present thesis aimed to determine the effects of the manipulation of training load and fatigue during RT on the acute neural changes and the chronic neural and functional adaptations on the untrained side. At the acute level, the overall results from the present thesis show that training load influences the acute increases in CSE in the trained but not the untrained side. Specifically, results suggest that stronger muscle contractions have a greater impact on corticospinal excitability. However, caution should be taken when inferring the effect of modification of training variables on long-term adaptations from those acute changes because there is no study showing any relation between acute changes and long-term functional or neural adaptations. In fact, despite the increase in CSE after high-load RT agrees with results of other studies (76-78, 258-260, 262, 263, 265), there are also studies showing no changes (31, 263) or reductions in CSE (261) immediately after a dynamic heavy-load RT with a training protocol compatible with the ones recommended by RT guidelines to

increase maximal voluntary force (442). It is unlikely that the training protocols used in those studies did not lead to increases in maximal voluntary force if repeated in time despite the acute decreases in CSE. Also, there are studies showing that the acute corticospinal response to unilateral RT could be enhanced by pacing the movement with a metronome auditory signal (76). However, chronic studies found that metronome-paced RT does not result in enhanced maximal voluntary force increases in the trained or the untrained limb (44, 336). Furthermore, in the second study of the present thesis we found a lack of modulation of the untrained hemisphere CSE or intracortical circuits after a single session of isometric RT, while several studies have shown that chronic unilateral isometric RT lead to long-term functional (325, 332, 333) and neural adaptations (325) in the untrained limb. Finally, in the third study of this thesis we found no changes in CSE of the RF and a decrease in the the CSE of the VL even after four weeks of high-load RT (436). This suggest that the acute increases in CSE that may be present after a single session of RT, as seen in the BB in the first and third study of this thesis (420, 443), do not necessarily lead to chronic increases in CSE accompanying voluntary force improvements. However, differences in the muscles tested and the training protocols used between the acute and the chronic studies of this thesis may have influenced the results (upper vs. lower limb). Indeed a recent study found that RT of the lower limbs do not increase corticospinal excitability after a single bout or after short-term RT (433), in contrast with several findings of acute increases in CSE after a single bout of RT in upper limb muscles (75-77, 257, 258, 420, 443). So, overall these results suggest an independence of long-term functional adaptations from the acute changes in CSE, which is not surprising given the lack of correlation even between chronic changes in CSE and maximal force adaptations in the trained or the untrained limb. Therefore other neural adaptations may be the mechanisms underlying voluntary force improvements other than just an increase in CSE.

At the chronic level, the results of the fourth study of the present thesis show that increases in maximal force in the untrained and trained leg occur only after high-load RT and are not affected by the magnitude of fatigue during training. Therefore, the results suggest that high levels of fatigue (muscle failure) in the trained side can be avoided during unilateral training, reducing exercise perceived effort and discomfort (444), muscle damage (430), and delayed day-to-

day recovery in the trained limb (430), with no detrimental effects on functional adaptations in the untrained limb.

X – CONCLUSIONS

X – CONCLUSIONS

STUDY 1

- The electromyographic responses and twitch forces evoked by transcranial magnetic stimulation (i.e.: MEPs) but not corticospinal tract stimulation (i.e.: CMEPs) of the biceps brachii increase in a load-dependent manner after an acute bout of resistance training.

- The selective influence of training load only on trasncranial magnetic stimulation responses suggest that the load-dependent effect is due to changes upstream of the α-motoneuron level and the motoneuronal-corticospinal synapse.

STUDY 2

- Although with high heterogeneity between studies, chronic unilateral resistance training leads to increased corticospinal excitability, reduced short-interval intracortical inhibition and silent period in the untrained M1, and reduced interhemispheric inhibition from the trained to the untrained hemisphere.

- Acute responses in the untrained hemisphere after unilateral resistance training are inconsistent

- Unilateral dynamic resistance training including eccentric contractions may enhance untrained hemisphere chronic adaptations due to a greater concurrent activation of the untrained hemisphere.

- Externally pacing the movement during unilateral resistance training enhances acute responses and chronic adaptations in the untrained hemisphere compared to self-paced movements.

- Evidence about the effects of training load and fatigue during resistance training on the untrained hemisphere acute responses and adaptations is scarce

STUDY 3

- The acute increases in corticospinal excitability in the trained limb occurred only after high-load isometric unilateral resistance training.

- Acute increases in corticospinal excitability in the trained limb were not related to changes in intracortical circuits and may be related to increases in corticospinal neurons excitability.

- The acute increases in corticospinal excitability after a session of unilateral isometric resistance training are limb-specific, as no change occurred in the untrained limb.

STUDY 4

- High-load resistance training but not higher levels of fatigue enhance neuromuscular adaptations in the trained and the untrained leg extensors.

- Maximal voluntary force improvements were not related to changes in corticospinal excitability.

XI – LIMITATIONS

XI – LIMITATIONS

STUDY 1

- The lack of a measurement of the MVC after each intervention prevents us from discarding the presence of fatigue and rule out its effect on the outcome measures.

- MEPs and CMEPs size were not matched therefore direct comparisons are not possible. However, the different time course of changes in MEPs and CMEPs allow to suggest that the load-dependent increase in MEPs was due to supraspinal mechanisms. However, future studies should match the size of MEPs and CMEPs to allow a more accurate determination of the site of neural changes after acute RT.

- The higher baseline size of the CMEPs could have reduced the potential for change after acute RT although it seems not likely based on previous studies in which CMEPs of larger baseline size increased to a greater extent than in the present study.

STUDY 2

- The differing TMS methodology (situation of measurement and stimulation parameters) used to study acute and chronic adaptations in the untrained hemisphere between studies could have contributed to the inconsistencies in the results, limiting the conclusions about the effects of training variables on the untrained hemisphere acute changes and adaptations.

- Other RT variables different from the discussed in the present review (e.g.: training volume, training frequency, muscles trained…) could also affect untrained hemisphere adaptations.

STUDY 3

- The stimulation intensity during paired-pulse protocols was not adjusted during POST measurements to match the pulse test MEP size to the size before training, which could have limited the changes in SICI or ICF.

- The stimulation intensity during contractions at 25% could have led to a MEP size close to its maximum size in BB, limiting the scope for change in this situation.

- The slowly ramped isometric contractions used results in relatively short periods of contraction at intensities above 50% of MVC, which could have limited the concurrent activation of the untrained hemisphere, reducing the potential for modulation of the untrained corticospinal tract.

STUDY 4

- The high training frequency (4d/wk.) choose to favour adaptations in the untrained leg extensors combined with training to concentric muscular failure could have had a cumulative effect leading to greater levels of muscle damage. This could have led to a decrease in the force-generating capacity of the trained leg that may have obscured neuromuscular adaptations.

XII – PRACTICAL APPLICATIONS

XII – PRACTICAL APPLICATIONS

The CE phenomenon as a result of unilateral RT has no relevance for a healthy person who could train both limbs with the main goal of increasing maximal voluntary force symmetrically. However, people with unilateral dysfunction due to stroke or orthopaedic injuries could benefit from unilateral RT as an adjuvant to standard rehabilitation programs (79, 81, 318, 319, 338, 410, 445, 446). 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.

The experimental data from the present thesis show that short-training periods with very low loads (25% of 1RM) do not lead to a CE effect and therefore high-loads are required to increase the force of the untrained leg extensors after four weeks of unilateral RT (436). From a practical point of view, the requirement of high-loads could limit the use of some exercises or materials during training. For example, rehabilitation programs usually include home-based exercise programs including exercises with portable materials such as elastic bands due to equipment limitations (341). By using this kind of material it could be difficult to obtain the required load for some exercises like leg extensions, which could be useful for unilateral leg bone's fractures or anterior cruciate ligament injuries, for example (319, 447). 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 initially hypothesized that one way of increasing the concurrent activation of the untrained hemisphere, which potentially represents the training stimulus that leads to the CE of voluntary force, is to increase the fatigue during the set, therefore reducing the requirements of high loads. However, our data shows that low-loads does not lead to a CE effect even when performed until concentric muscular failure. Even when performed with high-loads, no further benefits are obtained from training to failure when compared with a training protocol with equal volume in which sets are stopped away from failure (~50% of

total possible repetitions with a 75% of 1RM) (436). High levels of fatigue (reaching failure) during RT are associated with greater levels of muscle damage and delayed onset of muscle soreness (430), greater levels of perceived effort and discomfort during training (444, 448), and delayed day-to-day recovery (430). Those greater levels of discomfort during training and increased pain post-exercise, affecting delayed neuromuscular performance in the trained limb (i.e. non-injured or less affected limb), could be less tolerable, affecting the adherence of patients to rehabilitation programs (449). Therefore, training to concentric muscle failure during unilateral RT aiming to improve the maximal voluntary force of the untrained limb could be avoided in favour 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 (116, 117).

Additionally, the systematic review found that dynamic contractions, especially eccentric contractions, along with externally pacing the movement with auditory feedback, can enhance the adaptations in the untrained hemisphere in the form of increased CSE and decreased SICI and IHI (111). Notwithstanding the relationship of those changes with CE of voluntary muscle force is not clear (63). Eccentric contractions lead to a greater CE than concentric or isometric contractions (108, 109). Therefore, rehabilitation training programs using unilateral RT to obtain benefits in the untrained limb should preferentially include dynamic contractions incorporating eccentric contractions. However, despite externally-pacing the movement could enhance neural adaptations in the untrained hemisphere (44, 76, 336), it does not increase the magnitude of the CE effect compared to self-paced RT programs (336), casting doubts about the need to include externally-paced movements during rehabilitation programs. However, externally pacing the movement could help to emphasize the load control through the eccentric portion of the movement during not supervised training (i.e. home-based training programs) which is in fact more relevant for CE than pacing per-se.

By last, regarding the data of the studies looking at the effects of just one session of RT, our results show that the training load affect the acute increases in CSE in the trained side but not the untrained side, adding to the inconsistencies found in the systematic review regarding the effects of an acute session of unilateral RT on the untrained hemisphere (111, 420, 431). Therefore, our results

suggest that the corticospinal acute changes that have been suggested to trigger the neural adaptations in the untrained hemisphere leading to CE of voluntary force are not detectable after just one training session (431). Thus, results of acute studies should be interpreted with caution when trying to predict the effect of the manipulation of one training variable on the long-term functional and neural adaptations in the untrained sides.

XIII – FUTURE LINES OF INVESTIGATION

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The results of the present thesis are only applicable to healthy subjects and could not be extrapolated to patients. However, the CE phenomenon derived from unilateral RT is a model thought to be applied with patients unable to train bilaterally such as strokes or orthopaedic unilateral injuries. Those pathologies are associated with reductions in the excitability state of the brain controlling the affected limb (82-87). Therefore, modifications in training variables affecting untrained hemisphere activation could have different effects on CE in patients. For example, despite fatigue during the set does not further benefit CE in healthy adults (436), in which the excitability state of both cortices is normal, it could benefit subjects in which basal M1 excitability is inhibited, as occur in orthopaedic injuries (82-85). However, fatiguing RT may not be the best approach in neurologic patients with already high self-reported fatigue. Therefore, future research should focus on clinical trials aiming to determine which RT protocol might work better in different patients based on research on healthy subjects, such as the presented in this thesis and previous research.

Furthermore, in addition to clinical trials aiming to determine how CE could be optimized, there is a need to further determine who might benefit from CE. Clinical trials in stroke patients have found promising results regarding the application of unilateral RT as a tool to improve force in the more-affected limb (81, 88, 338). However, results regarding the utility of CE as an adjuvant to standard rehabilitation for orthopaedic injuries are contradictory (319, 445, 447, 450). Therefore, more clinical trials with patients are needed before stating the usefulness of unilateral RT to restore the force of the untrained more-affected limb.

In addition, even when the training protocol is optimized to increase CE, interlimb transfer of voluntary muscle force may be of small clinical relevance, still more in situations in which the excitability of the untrained hemisphere is impaired, as may occur in patients. Therefore, previous studies have tried to increase CE through increased sensory input to the untrained hemisphere, such as

mirror-training, whole body vibration or somatosensory electrical stimulation (89-91, 451, 452). However, the usefulness of these techniques to increase CE of voluntary muscle force has only been proved in healthy subjects and, when used in patients, it has been case reports (n = 1) (88) or focused more on skill training (453). The same occurs with techniques that increase the excitability of the M1, such as anodal transcranial direct current stimulation. This technique could enhance CE of voluntary muscle force in healthy adults by increasing the activation of the untrained hemisphere during unilateral contractions (92-94, 454). However, its utility has not been proved in patients. Therefore, future studies should prove in patients the utility of those strategies that increase CE in healthy subjects. In addition, although muscle force is relevant for many activities of daily living, motor skill should also be a target for CE. Therefore future CE research in patients should focus on how to combine RT and motor skill training to maximize the transfer of force and motor skill to the affected limb that allow a better functional recovery.

By last, CE of voluntary force seems to be related to adaptations in the untrained hemisphere induced by the simultaneous but lower activation of this hemisphere during forceful unilateral contractions (18, 64, 66-69). In some subjects, and under some circumstances like high-intensity contractions or long and fatiguing contractions, this concurrent activation of the untrained hemisphere leads to the inadvertent activation of the homologous resting muscles, a phenomenon called associated activity (208). Although participants are usually asked to actively relax the untrained limb, suppressing this associated activity (325), increases in maximal voluntary force in the untrained homologous muscles may be related or enhanced by this associated activity. It is thought that this associated activity could arise from the failure of a network of cortical areas that are involved in restricting the motor output to the contralateral muscles such as the supplementary motor area, dorsal premotor cortex, the anterior cingulate cortex or the precuneus (214-216, 455). In fact, when the dorsal premotor cortex is disturbed by repetitive TMS there is an increase in ipsilateral M1 excitability and associated activity in the resting homologous muscle during unilateral contractions of the contralateral muscle (214, 215). Therefore, future studies should focus on determining if temporal disruption of these key cortical areas

before unilateral RT could enhance the associated activity in the untrained muscles and therefore CE of voluntary muscle force.

XIV – MENCIÓN INTERNACIONAL

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Con el objetivo de cumplir con los criterios especificados en el Real Decreto 99/2011 para la obtención de la Mención Internacional en el Título de Doctor, se presentan las conclusiones del presente compendio de estudios en un idioma distinto al utilizado en la restante tesis.

ESTUDIO 1

- Las respuestas del bíceps braquial a la estimulación magnética transcraneal, pero no a la estimulación eléctrica del tracto corticoespinal, aumentaron tras un entrenamiento de fuerza en función de la intensidad de entrenamiento.

- La influencia selectiva de la intensidad de entrenamiento únicamente sobre las respuestas a la estimulación magnética transcraneal, sugiere que los mecanismos que provocan el aumento de la respuesta se sitúan por encima de las motoneuronas-α y de la sinapsis corticoespinal-motoneuronal.

ESTUDIO 2

- Aunque con una gran heterogeneidad entre estudios, el entrenamiento de fuerza unilateral provoca aumentos en la excitabilidad corticoespinal, disminuciones en la inhibición intracortical de corta latencia y el periodo de silencio en la corteza motora primaria no entrenada, y en la inhibición interhemisférica del hemisferio entrenado al no entrenado.

- Las respuestas agudas del hemisferio no entrenado tras una sesión de entrenamiento de fuerza son inconsistentes.

- El entrenamiento de fuerza dinámico incluyendo contracciones excéntricas podría aumentar las adaptaciones crónicas en el hemisferio no entrenado, probablemente debido a una mayor activación concurrente del mismo.

- Controlar el tempo de las contracciones de forma externa, con un metrónomo que emita señales auditivas, aumenta las respuestas agudas y las adaptaciones crónicas del hemisferio no entrenado en comparación a un tempo autorregulado.

- La evidencia sobre el efecto de la intensidad de entrenamiento de fuerza y la fatiga durante la serie sobre las adaptaciones en el hemisferio no entrenado es escasa.

ESTUDIO 3

- Los aumentos agudos en la excitabilidad corticospinal del miembro entrenado ocurren únicamente tras un entrenamiento de fuerza de alta intensidad.

- Los aumentos en la excitabilidad corticospinal del miembro entrenado no están vinculados a cambios en los circuitos intrcorticales y podrían deberse a aumentos en la excitabilidad de las neuronas corticoespinales.

- Los aumentos en la excitabilidad corticoespinal tras una sesión de entrenaiento de fuerza unilateral son específicos del miembro entrenado.

ESTUDIO 4

- El entrenamiento de fuerza de alta intensidad, pero no así niveles de fatiga mayores, aumentan las adaptaciones neuromusculares en los extensores de rodilla entrenados y no entrenados.

- Los aumentos de fuerza voluntaria en ambas piernas no están vinculados a aumentos en la excitabilidad corticoespinal.

XV - REFERENCES

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1. Lauersen JB, Andersen TE, Andersen LB. Strength training as superior, dose-dependent and safe prevention of acute and overuse sports injuries: a systematic review, qualitative analysis and meta-analysis. British journal of sports medicine. 2018.

2. Delecluse C. Influence of strength training on sprint running performance. Current findings and implications for training. Sports medicine (Auckland, NZ). 1997;24(3):147-56.

3. Alcaraz-Ibanez M, Rodriguez-Perez M. Effects of resistance training on performance in previously trained endurance runners: A systematic review. Journal of sports sciences. 2018;36(6):613-29.

4. Harrison PW, James LP, McGuigan MR, Jenkins DG, Kelly VG. Resistance Priming to Enhance Neuromuscular Performance in Sport: Evidence, Potential Mechanisms and Directions for Future Research. Sports Medicine. 2019;49(10):1499-514.

5. Engardt M, Knutsson E, Jonsson M, Sternhag M. Dynamic muscle strength training in stroke patients: effects on knee extension torque, electromyographic activity, and motor function. Archives of physical medicine and rehabilitation. 1995;76(5):419-25.

6. Strasser B, Siebert U, Schobersberger W. Resistance training in the treatment of the metabolic syndrome: a systematic review and meta-analysis of the effect of resistance training on metabolic clustering in patients with abnormal glucose metabolism. Sports medicine (Auckland, NZ). 2010;40(5):397-415.

7. Grontved A, Rimm EB, Willett WC, Andersen LB, Hu FB. A prospective study of weight training and risk of type 2 diabetes mellitus in men. Archives of internal medicine. 2012;172(17):1306-12.

8. Nagamatsu LS, Handy TC, Hsu CL, Voss M, Liu-Ambrose T. Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment. Archives of internal medicine. 2012;172(8):666-8.

9. Westcott WL. Resistance training is medicine: effects of strength training on health. Current sports medicine reports. 2012;11(4):209-16.

10. Grontved A, Pan A, Mekary RA, Stampfer M, Willett WC, Manson JE, et al. Muscle-strengthening and conditioning activities and risk of type 2 diabetes: a prospective study in two cohorts of US women. PLoS medicine. 2014;11(1):e1001587.

11. Codella R, Ialacqua M, Terruzzi I, Luzi L. May the force be with you: why resistance training is essential for subjects with type 2 diabetes mellitus without complications. Endocrine. 2018;62(1):14-25.

12. Gordon BR, McDowell CP, Hallgren M, Meyer JD, Lyons M, Herring MP. Association of efficacy of resistance exercise training with depressive symptoms: Meta-analysis and meta-regression analysis of randomized clinical trials. JAMA psychiatry. 2018;75(6):566-76.

13. Herold F, Törpel A, Schega L, Müller NG. Functional and/or structural brain changes in response to resistance exercises and resistance training lead to cognitive improvements - a systematic review. Eur Rev Aging Phys Act. 2019;16:10-.

14. Mcleod JC, Stokes T, Phillips SM. Resistance Exercise Training as a Primary Countermeasure to Age-Related Chronic Disease. Frontiers in Physiology. 2019;10(645).

15. Folland JP, Williams AG. The adaptations to strength training : morphological and neurological contributions to increased strength. Sports medicine (Auckland, NZ). 2007;37(2):145-68.

16. Benito PJ, Cupeiro R, Ramos-Campo DJ, Alcaraz PE, Rubio-Arias J. A Systematic Review with Meta-Analysis of the Effect of Resistance Training on Whole-Body Muscle Growth in Healthy Adult Males. International journal of environmental research and public health. 2020;17(4).

17. Green LA, Gabriel DA. The effect of unilateral training on contralateral limb strength in young, older, and patient populations: a meta-analysis of cross education. Physical Therapy Reviews. 2018:1-12.

18. Manca A, Dragone D, Dvir Z, Deriu F. Cross-education of muscular strength following unilateral resistance training: a meta-analysis. European journal of applied physiology. 2017;117(11):2335-54.

19. Munn J, Herbert RD, Gandevia SC. Contralateral effects of unilateral resistance training: a meta-analysis. Journal of applied physiology (Bethesda, Md : 1985). 2004;96(5):1861-6.

20. Scripture E.W. STL, and Brown E.M. On the education of muscular control and power. Studies from Yale Psycological Laboratory. 1894;2:114-9.

21. Houston ME, Froese EA, Valeriote SP, Green HJ, Ranney DA. Muscle performance, morphology and metabolic capacity during strength training and detraining: a one leg model. European journal of applied physiology and occupational physiology. 1983;51(1):25-35.

22. Ploutz LL, Tesch PA, Biro RL, Dudley GA. Effect of resistance training on muscle use during exercise. Journal of applied physiology (Bethesda, Md : 1985). 1994;76(4):1675-81.

23. Farthing JP, Borowsky R, Chilibeck PD, Binsted G, Sarty GE. Neuro-physiological adaptations associated with cross-education of strength. Brain topography. 2007;20(2):77-88.

24. Akima H, Takahashi H, Kuno SY, Masuda K, Masuda T, Shimojo H, et al. Early phase adaptations of muscle use and strength to isokinetic training. Medicine and science in sports and exercise. 1999;31(4):588-94.

25. Blazevich AJ, Gill ND, Deans N, Zhou S. Lack of human muscle architectural adaptation after short-term strength training. Muscle & nerve. 2007;35(1):78-86.

26. Enoka RM. Muscle strength and its development. New perspectives. Sports medicine (Auckland, NZ). 1988;6(3):146-68.

27. Sale DG. Neural adaptation to resistance training. Medicine and science in sports and exercise. 1988;20(5 Suppl):S135-45.

28. Zhou S. Chronic neural adaptations to unilateral exercise: mechanisms of cross education. Exercise and sport sciences reviews. 2000;28(4):177-84.

29. Carroll TJ, Riek S, Carson RG. Corticospinal responses to motor training revealed by transcranial magnetic stimulation. Exercise and sport sciences reviews. 2001;29(2):54-9.

30. Carroll TJ, Riek S, Carson RG. The sites of neural adaptation induced by resistance training in humans. The Journal of physiology. 2002;544(Pt 2):641-52.

31. Jensen JL, Marstrand PC, Nielsen JB. Motor skill training and strength training are associated with different plastic changes in the central nervous system. Journal of applied physiology (Bethesda, Md : 1985). 2005;99(4):1558-68.

32. Beck S, Taube W, Gruber M, Amtage F, Gollhofer A, Schubert M. Task-specific changes in motor evoked potentials of lower limb muscles after different training interventions. Brain research. 2007;1179:51-60.

33. Griffin L, Cafarelli E. Transcranial magnetic stimulation during resistance training of the tibialis anterior muscle. Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology. 2007;17(4):446-52.

34. Carroll TJ, Barton J, Hsu M, Lee M. The effect of strength training on the force of twitches evoked by corticospinal stimulation in humans. Acta physiologica (Oxford, England). 2009;197(2):161-73.

35. Hortobagyi T, Richardson SP, Lomarev M, Shamim E, Meunier S, Russman H, et al. Chronic low-frequency rTMS of primary motor cortex diminishes exercise training-induced gains in maximal voluntary force in humans. Journal of applied physiology (Bethesda, Md : 1985). 2009;106(2):403-11.

36. Lee M, Gandevia SC, Carroll TJ. Short-term strength training does not change cortical voluntary activation. Medicine and science in sports and exercise. 2009;41(7):1452-60.

37. Kidgell DJ, Pearce AJ. Corticospinal properties following short-term strength training of an intrinsic hand muscle. Human movement science. 2010;29(5):631-41.

38. Kidgell DJ, Stokes MA, Castricum TJ, Pearce AJ. Neurophysiological responses after short-term strength training of the biceps brachii muscle. Journal of strength and conditioning research / National Strength & Conditioning Association. 2010;24(11):3123-32.

39. Latella C, Kidgell DJ, Pearce AJ. Reduction in corticospinal inhibition in the trained and untrained limb following unilateral leg strength training. European journal of applied physiology. 2012;112(8):3097-107.

40. Weier AT, Pearce AJ, Kidgell DJ. Strength training reduces intracortical inhibition. Acta physiologica (Oxford, England). 2012;206(2):109-19.

41. Christie A, Kamen G. Cortical inhibition is reduced following short-term training in young and older adults. Age (Dordrecht, Netherlands). 2014;36(2):749-58.

42. Iglesias-Soler E, Mayo X, Río Rodríguez D, Carballeira E, Fariñas J, Fernández-Del-Olmo M. Inter-repetition rest training and traditional set configuration produce similar strength gains without cortical adaptations. Journal of sports sciences. 2015;34(15):1473-84.

43. Giboin LS, Weiss B, Thomas F, Gruber M. Neuroplasticity following short-term strength training occurs at supraspinal level and is specific for the trained task. Acta physiologica (Oxford, England). 2017.

44. Leung M, Rantalainen T, Teo WP, Kidgell D. The corticospinal responses of metronome-paced, but not self-paced strength training are similar to motor skill training. European journal of applied physiology. 2017.

45. Mason J, Frazer A, Horvath DM, Pearce AJ, Avela J, Howatson G, et al. Adaptations in corticospinal excitability and inhibition are not spatially confined to the agonist muscle following strength training. European journal of applied physiology. 2017;117(7):1359-71.

46. Tallent J, Goodall S, Gibbon KC, Hortobágyi T, Howatson G. Enhanced Corticospinal Excitability and Volitional Drive in Response to Shortening and Lengthening Strength Training and Changes Following Detraining. Front Physiol. 2017;8.

47. Nuzzo JL, Barry BK, Jones MD, Gandevia SC, Taylor JL. Effects of Four Weeks of Strength Training on the Corticomotoneuronal Pathway. Medicine and science in sports and exercise. 2017;49(11):2286-96.

48. Taylor JL, Gandevia SC. Noninvasive stimulation of the human corticospinal tract. Journal of applied physiology (Bethesda, Md : 1985). 2004;96(4):1496-503.

49. Aagaard P, Simonsen EB, Andersen JL, Magnusson P, Dyhre-Poulsen P. Neural adaptation to resistance training: changes in evoked V-wave and H-reflex responses. Journal of applied physiology (Bethesda, Md : 1985). 2002;92(6):2309-18.

50. Zehr EP. Training-induced adaptive plasticity in human somatosensory reflex pathways. Journal of Applied Physiology. 2006;101(6):1783-94.

51. Del Balso C, Cafarelli E. Adaptations in the activation of human skeletal muscle induced by short-term isometric resistance training. Journal of applied physiology (Bethesda, Md : 1985). 2007;103(1):402-11.

52. Gruber M, Taube W, Gollhofer A, Beck S, Amtage F, Schubert M. Training-specific adaptations of H- and stretch reflexes in human soleus muscle. Journal of motor behavior. 2007;39(1):68-78.

53. Holtermann A, Roeleveld K, Engstrom M, Sand T. Enhanced H-reflex with resistance training is related to increased rate of force development. European journal of applied physiology. 2007;101(3):301-12.

54. Duclay J, Martin A, Robbe A, Pousson M. Spinal reflex plasticity during maximal dynamic contractions after eccentric training. Medicine and science in sports and exercise. 2008;40(4):722-34.

55. Fimland MS, Helgerud J, Solstad GM, Iversen VM, Leivseth G, Hoff J. Neural adaptations underlying cross-education after unilateral strength training. European journal of applied physiology. 2009;107(6):723-30.

56. Ekblom MM. Improvements in dynamic plantar flexor strength after resistance training are associated with increased voluntary activation and V-to-M ratio. Journal of applied physiology (Bethesda, Md : 1985). 2010;109(1):19-26.

57. Vila-Cha C, Falla D, Correia MV, Farina D. Changes in H reflex and V wave following short-term endurance and strength training. Journal of applied physiology (Bethesda, Md : 1985). 2012;112(1):54-63.

58. Barrue-Belou S, Amarantini D, Marque P, Duclay J. Neural adaptations to submaximal isokinetic eccentric strength training. European journal of applied physiology. 2016;116(5):1021-30.

59. Colomer-Poveda D, Romero-Arenas S, Vera-Ibanez A, Vinuela-Garcia M, Marquez G. Effects of 4 weeks of low-load unilateral resistance training, with and without blood flow restriction, on strength, thickness, V wave, and H reflex of the soleus muscle in men. European journal of applied physiology. 2017;117(7):1339-47.

60. Carroll TJ, Selvanayagam VS, Riek S, Semmler JG. Neural adaptations to strength training: moving beyond transcranial magnetic stimulation and reflex studies. Acta physiologica (Oxford, England). 2011;202(2):119-40.

61. Adkins DL, Boychuk J, Remple MS, Kleim JA. Motor training induces experience-specific patterns of plasticity across motor cortex and spinal cord. Journal of applied physiology (Bethesda, Md : 1985). 2006;101(6):1776-82.

62. Siddique U, Rahman S, Frazer AK, Pearce AJ, Howatson G, Kidgell DJ. Determining the Sites of Neural Adaptations to Resistance Training: A Systematic Review and Meta-analysis. Sports medicine (Auckland, NZ). 2020:10.1007/s40279-020-01258-z.

63. Manca A, Hortobagyi T, Rothwell JC, Deriu F. Neurophysiological adaptations in the untrained side in conjunction with cross-education of muscle strength: a systematic review and meta-analysis. Journal of applied physiology (Bethesda, Md : 1985). 2018;124(6):1502-18.

64. Frazer AK, Pearce AJ, Howatson G, Thomas K, Goodall S, Kidgell DJ. Determining the potential sites of neural adaptation to cross-education: implications for the cross-education of muscle strength. European journal of applied physiology. 2018;118(9):1751-72.

65. Hendy AM, Lamon S. The Cross-Education Phenomenon: Brain and Beyond. Frontiers in Physiology. 2017;8(297).

66. Ruddy KL, Carson RG. Neural pathways mediating cross education of motor function. Frontiers in human neuroscience. 2013;7:397.

67. Lee M, Carroll TJ. Cross education: possible mechanisms for the contralateral effects of unilateral resistance training. Sports medicine (Auckland, NZ). 2007;37(1):1-14.

68. Carroll TJ, Herbert RD, Munn J, Lee M, Gandevia SC. Contralateral effects of unilateral strength training: evidence and possible mechanisms. Journal of applied physiology (Bethesda, Md : 1985). 2006;101(5):1514-22.

69. Hortobagyi T. Cross education and the human central nervous system. IEEE engineering in medicine and biology magazine : the quarterly magazine of the Engineering in Medicine & Biology Society. 2005;24(1):22-8.

70. Hortobagyi T, Taylor JL, Petersen NT, Russell G, Gandevia SC. Changes in segmental and motor cortical output with contralateral muscle contractions and altered sensory inputs in humans. Journal of neurophysiology. 2003;90(4):2451-9.

71. Liu JZ, Shan ZY, Zhang LD, Sahgal V, Brown RW, Yue GH. Human brain activation during sustained and intermittent submaximal fatigue muscle contractions: an FMRI study. Journal of neurophysiology. 2003;90(1):300-12.

72. Buetefisch CM, Revill KP, Shuster L, Hines B, Parsons M. Motor demand-dependent activation of ipsilateral motor cortex. Journal of neurophysiology. 2014;112(4):999-1009.

73. Dai TH, Liu JZ, Sahgal V, Brown RW, Yue GH. Relationship between muscle output and functional MRI-measured brain activation. Experimental brain research. 2001;140(3):290-300.

74. 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.

75. Selvanayagam VS, Riek S, Carroll TJ. Early neural responses to strength training. Journal of applied physiology (Bethesda, Md : 1985). 2011;111(2):367-75.

76. Leung M, Rantalainen T, Teo WP, Kidgell D. Motor cortex excitability is not differentially modulated following skill and strength training. Neuroscience. 2015;305:99-108.

77. Nuzzo JL, Barry BK, Gandevia SC, Taylor JL. Acute Strength Training Increases Responses to Stimulation of Corticospinal Axons. Medicine and science in sports and exercise. 2016;48(1):139-50.

78. Latella C, Hendy A, Vanderwesthuizen D, Teo WP. The modulation of corticospinal excitability and inhibition following acute resistance exercise in males and females. European journal of sport science. 2018;18(7):984-93.

79. Farthing JP, Zehr EP. Restoring symmetry: clinical applications of cross-education. Exercise and sport sciences reviews. 2014;42(2):70-5.

80. Hendy AM, Spittle M, Kidgell DJ. Cross education and immobilisation: mechanisms and implications for injury rehabilitation. Journal of science and medicine in sport / Sports Medicine Australia. 2012;15(2):94-101.

81. Ehrensberger M, Simpson D, Broderick P, Monaghan K. Cross-education of strength has a positive impact on post-stroke rehabilitation: a systematic literature review. Topics in stroke rehabilitation. 2016;23(2):126-35.

82. Needle AR, Lepley AS, Grooms DR. Central Nervous System Adaptation After Ligamentous Injury: a Summary of Theories, Evidence, and Clinical Interpretation. Sports medicine (Auckland, NZ). 2016.

83. Pietrosimone BG, Lepley AS, Ericksen HM, Clements A, Sohn DH, Gribble PA. Neural Excitability Alterations After Anterior Cruciate Ligament Reconstruction. Journal of athletic training. 2015;50(6):665-74.

84. Lepley AS, Gribble PA, Thomas AC, Tevald MA, Sohn DH, Pietrosimone BG. Quadriceps neural alterations in anterior cruciate ligament reconstructed patients: A 6-month longitudinal investigation. Scandinavian journal of medicine & science in sports. 2015;25(6):828-39.

85. Kapreli E, Athanasopoulos S, Gliatis J, Papathanasiou M, Peeters R, Strimpakos N, et al. Anterior cruciate ligament deficiency causes brain plasticity: a functional MRI study. The American journal of sports medicine. 2009;37(12):2419-26.

86. Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. Annals of neurology. 2004;55(3):400-9.

87. Traversa R, Cicinelli P, Bassi A, Rossini PM, Bernardi G. Mapping of motor cortical reorganization after stroke. A brain stimulation study with focal magnetic pulses. Stroke; a journal of cerebral circulation. 1997;28(1):110-7.

88. Simpson D, Ehrensberger M, Broderick P, Horgan F, Blake C, Roberts D, et al. Cross-education plus mirror therapy as a post-stroke rehabilitation intervention: A case study2019. 51-7 p.

89. Zult T, Goodall S, Thomas K, Solnik S, Hortobagyi T, Howatson G. Mirror Training Augments the Cross-education of Strength and Affects Inhibitory Paths. Medicine and science in sports and exercise. 2016;48(6):1001-13.

90. Goodwill AM, Kidgell DJ. The effects of whole-body vibration on the cross-transfer of strength. TheScientificWorldJournal. 2012;2012:504837.

91. Veldman MP, Maffiuletti NA, Hallett M, Zijdewind I, Hortobagyi T. Direct and crossed effects of somatosensory stimulation on neuronal excitability and motor performance in humans. Neuroscience and biobehavioral reviews. 2014;47:22-35.

92. Frazer AK, Williams J, Spittle M, Kidgell DJ. Cross-education of muscular strength is facilitated by homeostatic plasticity. European journal of applied physiology. 2017;117(4):665-77.

93. Hendy AM, Teo WP, Kidgell DJ. Anodal Transcranial Direct Current Stimulation Prolongs the Cross-education of Strength and Corticomotor Plasticity. Medicine and science in sports and exercise. 2015;47(9):1788-97.

94. Hendy AM, Kidgell DJ. Anodal-tDCS applied during unilateral strength training increases strength and corticospinal excitability in the untrained homologous muscle. Experimental brain research. 2014;232(10):3243-52.

95. Lasevicius T, Ugrinowitsch C, Schoenfeld BJ, Roschel H, Tavares LD, De Souza EO, et al. Effects of different intensities of resistance training with equated volume load on muscle strength and hypertrophy. European journal of sport science. 2018:1-9.

96. Schoenfeld BJ, Grgic J, Ogborn D, Krieger JW. Strength and hypertrophy adaptations between low- versus high-load resistance training: A systematic review and meta-analysis. Journal of strength and conditioning research / National Strength & Conditioning Association. 2017;31(12):3508.

97. Jenkins NDM, Miramonti AA, Hill EC, Smith CM, Cochrane-Snyman KC, Housh TJ, et al. Greater Neural Adaptations following High- vs. Low-Load Resistance Training. Front Physiol. 2017;8:331.

98. Ralston GW, Kilgore L, Wyatt FB, Baker JS. The Effect of Weekly Set Volume on Strength Gain: A Meta-Analysis. Sports medicine (Auckland, NZ). 2017;47(12):2585-601.

99. Radaelli R, Fleck SJ, Leite T, Leite RD, Pinto RS, Fernandes L, et al. Dose-response of 1, 3, and 5 sets of resistance exercise on strength, local muscular endurance, and hypertrophy. Journal of strength and conditioning research / National Strength & Conditioning Association. 2015;29(5):1349-58.

100. Borde R, Hortobagyi T, Granacher U. Dose-Response Relationships of Resistance Training in Healthy Old Adults: A Systematic Review and Meta-Analysis. Sports medicine (Auckland, NZ). 2015;45(12):1693-720.

101. Grgic J, Schoenfeld BJ, Davies TB, Lazinica B, Krieger JW, Pedisic Z. Effect of Resistance Training Frequency on Gains in Muscular Strength: A Systematic Review and Meta-Analysis. Sports medicine (Auckland, NZ). 2018.

102. Gomes GK, Franco CM, Nunes PRP, Orsatti FL. High-frequency resistance training is not more effective than low-frequency resistance training in increasing muscle mass and strength in well-trained men. Journal of strength and conditioning research / National Strength & Conditioning Association. 2018.

103. Pareja-Blanco F, Rodriguez-Rosell D, Sanchez-Medina L, Sanchis-Moysi J, Dorado C, Mora-Custodio R, et al. Effects of velocity loss during resistance training on athletic performance, strength gains and muscle adaptations. Scandinavian journal of medicine & science in sports. 2017;27(7):724-35.

104. Izquierdo M, Ibanez J, Gonzalez-Badillo JJ, Hakkinen K, Ratamess NA, Kraemer WJ, et al. Differential effects of strength training leading to failure versus not to failure on hormonal responses, strength, and muscle power gains. Journal of applied physiology (Bethesda, Md : 1985). 2006;100(5):1647-56.

105. Drinkwater EJ, Lawton TW, Lindsell RP, Pyne DB, Hunt PH, McKenna MJ. Training leading to repetition failure enhances bench press strength gains in elite junior athletes. Journal of strength and conditioning research. 2005;19(2):382-8.

106. Folland JP, Irish CS, Roberts JC, Tarr JE, Jones DA. Fatigue is not a necessary stimulus for strength gains during resistance training. British journal of sports medicine. 2002;36(5):370-3; discussion 4.

107. Rooney KJ, Herbert RD, Balnave RJ. Fatigue contributes to the strength training stimulus. Medicine and science in sports and exercise. 1994;26(9):1160-4.

108. Hortobagyi T, Lambert NJ, Hill JP. Greater cross education following training with muscle lengthening than shortening. Medicine and science in sports and exercise. 1997;29(1):107-12.

109. Kidgell DJ, Frazer AK, Daly RM, Rantalainen T, Ruotsalainen I, Ahtiainen J, et al. Increased cross-education of muscle strength and reduced corticospinal inhibition following eccentric strength training. Neuroscience. 2015;300:566-75.

110. Munn J, Herbert RD, Hancock MJ, Gandevia SC. Training with unilateral resistance exercise increases contralateral strength. Journal of applied physiology (Bethesda, Md : 1985). 2005;99(5):1880-4.

111. Colomer-Poveda D, Romero-Arenas S, Keller M, Hortobagyi T, Marquez G. Effects of acute and chronic unilateral resistance training variables on ipsilateral motor cortical excitability and cross-education: A systematic review. Physical therapy in sport : official journal of the Association of Chartered Physiotherapists in Sports Medicine. 2019;40:143-52.

112. Howatson G, Taylor MB, Rider P, Motawar BR, McNally MP, Solnik S, et al. Ipsilateral motor cortical responses to TMS during lengthening and shortening of the contralateral wrist flexors. The European journal of neuroscience. 2011;33(5):978-90.

113. Uematsu A, Obata H, Endoh T, Kitamura T, Hortobagyi T, Nakazawa K, et al. Asymmetrical modulation of corticospinal excitability in the contracting and resting contralateral wrist flexors during unilateral shortening, lengthening and isometric contractions. Experimental brain research. 2010;206(1):59-69.

114. Dettmers C, Fink GR, Lemon RN, Stephan KM, Passingham RE, Silbersweig D, et al. Relation between cerebral activity and force in the motor areas of the human brain. Journal of neurophysiology. 1995;74(2):802-15.

115. Perez MA, Cohen LG. Mechanisms underlying functional changes in the primary motor cortex ipsilateral to an active hand. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2008;28(22):5631-40.

116. Hinkle JL, Becker KJ, Kim JS, Choi-Kwon S, Saban KL, McNair N, et al. Poststroke Fatigue: Emerging Evidence and Approaches to Management: A Scientific Statement for Healthcare Professionals From the American Heart Association. Stroke; a journal of cerebral circulation. 2017;48(7):e159-e70.

117. Braley TJ, Chervin RD. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. Sleep. 2010;33(8):1061-7.

118. Taube W. "What trains together, gains together": strength training strengthens not only muscles but also neural networks. Journal of applied physiology (Bethesda, Md : 1985). 2011;111(2):347-8.

119. Bartholow R. Experiments on the Functions of the Human Brain. Br Med J. 1874;1(700):727-.

120. Penfield W. The excitable cortex in conscious man. Liverpool; Atlantic Highlands, N.J.: Liverpool University Press ; Distributed in the U.S.A. by Humanities Press; 1967.

121. Penfield W, Jasper HH, Penfield W. Epilepsy and the functional anatomy of the human brain. Boston: Little, Brown; 1954.

122. Merton PA, Hill DK, Morton HB, Marsden CD. Scope of a technique for electrical stimulation of human brain, spinal cord, and muscle. Lancet (London, England). 1982;2(8298):597-600.

123. Merton PA, Morton HB. Stimulation of the cerebral cortex in the intact human subject. Nature. 1980;285(5762):227-.

124. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet (London, England). 1985;1(8437):1106-7.

125. Barker AT, Freeston IL, Jabinous R, Jarratt JA. Clinical evaluation of conduction time measurements in central motor pathways using magnetic stimulation of human brain. Lancet (London, England). 1986;1(8493):1325-6.

126. Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. The Lancet Neurology. 2003;2(3):145-56.

127. Rothwell J, Thompson P, Day B, Boyd S, Marsden C. Stimulation of the human motor cortex through the scalp. Experimental physiology. 1991;76(2):159-200.

128. Barker AT. An introduction to the basic principles of magnetic nerve stimulation. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society. 1991;8(1):26-37.

129. Rösler KM, Hess CW, Heckmann R, Ludin HP. Significance of shape and size of the stimulating coil in magnetic stimulation of the human motor cortex. Neuroscience letters. 1989;100(1-3):347-52.

130. Hallett M. Transcranial magnetic stimulation and the human brain. Nature. 2000;406(6792):147-50.

131. Roth Y, Zangen A, Hallett M. A coil design for transcranial magnetic stimulation of deep brain regions. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society. 2002;19(4):361-70.

132. Day BL, Thompson PD, Dick JP, Nakashima K, Marsden CD. Different sites of action of electrical and magnetic stimulation of the human brain. Neuroscience letters. 1987;75(1):101-6.

133. Di Lazzaro V, Oliviero A, Profice P, Saturno E, Pilato F, Insola A, et al. Comparison of descending volleys evoked by transcranial magnetic and electric stimulation in conscious humans. Electroencephalography and clinical neurophysiology. 1998;109(5):397-401.

134. Di Lazzaro V, Rothwell JC. Corticospinal activity evoked and modulated by non-invasive stimulation of the intact human motor cortex. The Journal of physiology. 2014;592(19):4115-28.

135. Day BL, Dressler D, Maertens de Noordhout A, Marsden CD, Nakashima K, Rothwell JC, et al. Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. The Journal of physiology. 1989;412:449-73.

136. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiological reviews. 2001;81(4):1725-89.

137. McNeil CJ, Butler JE, Taylor JL, Gandevia SC. Testing the excitability of human motoneurons. Frontiers in human neuroscience. 2013;7.

138. Rodriguez-Falces J, Place N. Determinants, analysis and interpretation of the muscle compound action potential (M wave) in humans: implications for the study of muscle fatigue. European journal of applied physiology. 2017.

139. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2015;126(6):1071-107.

140. Inghilleri M, Berardelli A, Cruccu G, Manfredi M. Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. The Journal of physiology. 1993;466:521-34.

141. Skarabot J, Mesquita RNO, Brownstein CG, Ansdell P. Myths and Methodologies: How loud is the story told by the transcranial magnetic stimulation-evoked silent period? Experimental physiology. 2019;104(5):635-42.

142. Chen R, Lozano AM, Ashby P. Mechanism of the silent period following transcranial magnetic stimulation. Evidence from epidural recordings. Experimental brain research. 1999;128(4):539-42.

143. Garry MI, Thomson RH. The effect of test TMS intensity on short-interval intracortical inhibition in different excitability states. Experimental brain research. 2009;193(2):267-74.

144. Chen R. Interactions between inhibitory and excitatory circuits in the human motor cortex. Experimental brain research. 2004;154(1):1-10.

145. Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, et al. Corticocortical inhibition in human motor cortex. The Journal of physiology. 1993;471:501-19.

146. Di Lazzaro V, Oliviero A, Meglio M, Cioni B, Tamburrini G, Tonali P, et al. Direct demonstration of the effect of lorazepam on the excitability of the human motor cortex. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2000;111(5):794-9.

147. Ziemann U, Chen R, Cohen LG, Hallett M. Dextromethorphan decreases the excitability of the human motor cortex. Neurology. 1998;51(5):1320-4.

148. Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD. Interhemispheric inhibition of the human motor cortex. The Journal of physiology. 1992;453:525-46.

149. Perez MA, Cohen LG. Interhemispheric inhibition between primary motor cortices: what have we learned? The Journal of physiology. 2009;587(Pt 4):725-6.

150. Reis J, Swayne OB, Vandermeeren Y, Camus M, Dimyan MA, Harris-Love M, et al. Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. The Journal of physiology. 2008;586(2):325-51.

151. Sherrington CS. The integrative action of the nervous system. New Haven: Yale University Press; 1961.

152. Heckman C, Mottram C, Quinlan K, Theiss R, Koschnitzky J. Motoneuron excitability: The importance of neuromodulatory inputs. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2009;120:2040-54.

153. Taylor JL. Stimulation at the cervicomedullary junction in human subjects. Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology. 2006;16(3):215-23.

154. Ugawa Y, Rothwell JC, Day BL, Thompson PD, Marsden CD. Percutaneous electrical stimulation of corticospinal pathways at the level of the pyramidal decussation in humans. Annals of neurology. 1991;29(4):418-27.

155. Taylor JL, Petersen NT, Butler JE, Gandevia SC. Interaction of transcranial magnetic stimulation and electrical transmastoid stimulation in human subjects. The Journal of physiology. 2002;541(Pt 3):949-58.

156. Martin PG, Butler JE, Gandevia SC, Taylor JL. Noninvasive stimulation of human corticospinal axons innervating leg muscles. Journal of neurophysiology. 2008;100(2):1080-6.

157. Škarabot J, Ansdell P, Brownstein CG, Thomas K, Howatson G, Goodall S, et al. Electrical stimulation of human corticospinal axons at the level of the lumbar spinal segments. European Journal of Neuroscience. 2019;49(10):1254-67.

158. Petersen NT, Taylor JL, Gandevia SC. The effect of electrical stimulation of the corticospinal tract on motor units of the human biceps brachii. The Journal of physiology. 2002;544(Pt 1):277-84.

159. Vigotsky AD, Halperin I, Lehman GJ, Trajano GS, Vieira TM. Interpreting Signal Amplitudes in Surface Electromyography Studies in Sport and Rehabilitation Sciences. Frontiers in Physiology. 2018;8(985).

160. Schieppati M. The Hoffmann reflex: a means of assessing spinal reflex excitability and its descending control in man. Progress in neurobiology. 1987;28(4):345-76.

161. Zehr EP. Considerations for use of the Hoffmann reflex in exercise studies. European journal of applied physiology. 2002;86(6):455-68.

162. Hoffmann P. Beitrag zur Kenntnis der menschlichen Reflexemit besonderer Berucksichtigung der elektrischen Erscheinun-gen. Arch Anat Physiol 1910;1:223-46.

163. Hoffmann P. Uber die Beziehungen der Sehnenreflexe zurwillkurlichen Bewegung und zum Tonus. . Z Biol 1918;68:351-70.

164. Palmieri RM, Ingersoll CD, Hoffman MA. The Hoffmann Reflex: Methodologic Considerations and Applications for Use in Sports Medicine and Athletic Training Research. Journal of athletic training. 2004;39(3):268-77.

165. Upton AR, McComas AJ, Sica RE. Potentiation of "late" responses evoked in muscles during effort. Journal of neurology, neurosurgery, and psychiatry. 1971;34(6):699-711.

166. Nuzzo JL, Trajano GS, Barry BK, Gandevia SC, Taylor JL. Arm posture-dependent changes in corticospinal excitability are largely spinal in origin. Journal of neurophysiology. 2016;115(4):2076-82.

167. Collins BW, Cadigan EWJ, Stefanelli L, Button DC. Corticospinal excitability of the biceps brachii is shoulder position dependent. Journal of neurophysiology. 2017;118(6):3242-51.

168. Gerloff C, Corwell B, Chen R, Hallett M, Cohen LG. The role of the human motor cortex in the control of complex and simple finger movement sequences. Brain : a journal of neurology. 1998;121 (Pt 9):1695-709.

169. Rao SM, Binder JR, Bandettini PA, Hammeke TA, Yetkin FZ, Jesmanowicz A, et al. Functional magnetic resonance imaging of complex human movements. Neurology. 1993;43(11):2311-8.

170. Jenkins IH, Passingham RE, Brooks DJ. The effect of movement frequency on cerebral activation: a positron emission tomography study. Journal of the neurological sciences. 1997;151(2):195-205.

171. Fang Y, Siemionow V, Sahgal V, Xiong F, Yue GH. Distinct brain activation patterns for human maximal voluntary eccentric and concentric muscle actions. Brain research. 2004;1023(2):200-12.

172. Fang Y, Siemionow V, Sahgal V, Xiong F, Yue GH. Greater movement-related cortical potential during human eccentric versus concentric muscle contractions. Journal of neurophysiology. 2001;86(4):1764-72.

173. Kernell D, Electronic Book C. The motoneurone and its muscle fibres. 2006.

174. Henneman E, Clamann HP, Gillies JD, Skinner RD. Rank order of motoneurons within a pool: law of combination. Journal of neurophysiology. 1974;37(6):1338-49.

175. Petersen NC, Butler JE, Taylor JL, Gandevia SC. Probing the corticospinal link between the motor cortex and motoneurones: some neglected

aspects of human motor cortical function. Acta physiologica (Oxford, England). 2010;198(4):403-16.

176. Ugawa Y, Terao Y, Hanajima R, Sakai K, Kanazawa I. Facilitatory effect of tonic voluntary contraction on responses to motor cortex stimulation. Electroencephalography and clinical neurophysiology. 1995;97(6):451-4.

177. Taylor JL, Allen GM, Butler JE, Gandevia SC. Effect of contraction strength on responses in biceps brachii and adductor pollicis to transcranial magnetic stimulation. Experimental brain research. 1997;117(3):472-8.

178. Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, et al. Effects of voluntary contraction on descending volleys evoked by transcranial stimulation in conscious humans. The Journal of physiology. 1998;508 (Pt 2):625-33.

179. Martin PG, Gandevia SC, Taylor JL. Output of human motoneuron pools to corticospinal inputs during voluntary contractions. Journal of neurophysiology. 2006;95(6):3512-8.

180. Skarabot J, Tallent J, Goodall S, Durbaba R, Howatson G. Corticospinal excitability during shortening and lengthening actions with incremental torque output. Experimental physiology. 2018;103(12):1586-92.

181. Perez MA, Cohen LG. Scaling of motor cortical excitability during unimanual force generation. Cortex. 2009;45(9):1065-71.

182. Gelli F, Del Santo F, Popa T, Mazzocchio R, Rossi A. Factors influencing the relation between corticospinal output and muscle force during voluntary contractions. The European journal of neuroscience. 2007;25(11):3469-75.

183. Goodall S, Romer LM, Ross EZ. Voluntary activation of human knee extensors measured using transcranial magnetic stimulation. Experimental physiology. 2009;94(9):995-1004.

184. Jones KE, Bawa P. Computer simulation of the responses of human motoneurons to composite 1A EPSPS: effects of background firing rate. Journal of neurophysiology. 1997;77(1):405-20.

185. Matthews PB. The effect of firing on the excitability of a model motoneurone and its implications for cortical stimulation. The Journal of physiology. 1999;518 (Pt 3)(Pt 3):867-82.

186. Milner-Brown HS, Stein RB, Yemm R. Changes in firing rate of human motor units during linearly changing voluntary contractions. The Journal of physiology. 1973;230(2):371-90.

187. Kukulka CG, Clamann HP. Comparison of the recruitment and discharge properties of motor units in human brachial biceps and adductor pollicis during isometric contractions. Brain research. 1981;219(1):45-55.

188. Oya T, Hoffman BW, Cresswell AG. Corticospinal-evoked responses in lower limb muscles during voluntary contractions at varying strengths. Journal of applied physiology (Bethesda, Md : 1985). 2008;105(5):1527-32.

189. Brownstein CG, Ansdell P, Skarabot J, Howatson G, Goodall S, Thomas K. An optimal protocol for measurement of corticospinal excitability, short intracortical inhibition and intracortical facilitation in the rectus femoris. Journal of the neurological sciences. 2018;394:45-56.

190. Ortu E, Deriu F, Suppa A, Tolu E, Rothwell JC. Effects of volitional contraction on intracortical inhibition and facilitation in the human motor cortex. The Journal of physiology. 2008;586(Pt 21):5147-59.

191. Zoghi M, Nordstrom MA. Progressive suppression of intracortical inhibition during graded isometric contraction of a hand muscle is not influenced by hand preference. Experimental brain research. 2007;177(2):266-74.

192. Floeter MK, Rothwell JC. Releasing the brakes before pressing the gas pedal. Neurology. 1999;53(4):664-5.

193. van Duinen H, Renken R, Maurits NM, Zijdewind I. Relation between muscle and brain activity during isometric contractions of the first dorsal interosseus muscle. Human brain mapping. 2008;29(3):281-99.

194. Sergio LE, Hamel-Pâquet C, Kalaska JF. Motor cortex neural correlates of output kinematics and kinetics during isometric-force and arm-reaching tasks. Journal of neurophysiology. 2005;94(4):2353-78.

195. Evarts EV. Relation of pyramidal tract activity to force exerted during voluntary movement. Journal of neurophysiology. 1968;31(1):14-27.

196. Ashe J. Force and the motor cortex. Behavioural brain research. 1997;87(2):255-69.

197. Hatsopoulos NG. Encoding in the Motor Cortex: Was Evarts Right After All? Focus on "Motor Cortex Neural Correlates of Output Kinematics and

Kinetics During Isometric-Force and Arm-Reaching Tasks". Journal of neurophysiology. 2005;94(4):2261-2.

198. Stedman A, Davey NJ, Ellaway PH. Facilitation of human first dorsal interosseous muscle responses to transcranial magnetic stimulation during voluntary contraction of the contralateral homonymous muscle. Muscle & nerve. 1998;21(8):1033-9.

199. Muellbacher W, Facchini S, Boroojerdi B, Hallett M. Changes in motor cortex excitability during ipsilateral hand muscle activation in humans. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2000;111(2):344-9.

200. Hess CW, Mills KR, Murray NM. Magnetic stimulation of the human brain: facilitation of motor responses by voluntary contraction of ipsilateral and contralateral muscles with additional observations on an amputee. Neuroscience letters. 1986;71(2):235-40.

201. Meyer BU, Roricht S, Grafin von Einsiedel H, Kruggel F, Weindl A. Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. Brain : a journal of neurology. 1995;118 (Pt 2):429-40.

202. Kobayashi M, Hutchinson S, Schlaug G, Pascual-Leone A. Ipsilateral motor cortex activation on functional magnetic resonance imaging during unilateral hand movements is related to interhemispheric interactions. NeuroImage. 2003;20(4):2259-70.

203. Kristeva R, Cheyne D, Deecke L. Neuromagnetic fields accompanying unilateral and bilateral voluntary movements: topography and analysis of cortical sources. Electroencephalography and clinical neurophysiology. 1991;81(4):284-98.

204. Devine KL, LeVeau BF, Yack HJ. Electromyographic activity recorded from an unexercised muscle during maximal isometric exercise of the contralateral agonists and antagonists. Physical therapy. 1981;61(6):898-903.

205. Dimitrijevic MR, McKay WB, Sarjanovic I, Sherwood AM, Svirtlih L, Vrbova G. Co-activation of ipsi- and contralateral muscle groups during contraction of ankle dorsiflexors. Journal of the neurological sciences. 1992;109(1):49-55.

206. Zijdewind I, Kernell D. Bilateral interactions during contractions of intrinsic hand muscles. Journal of neurophysiology. 2001;85(5):1907-13.

207. Aranyi Z, Rosler KM. Effort-induced mirror movements. A study of transcallosal inhibition in humans. Experimental brain research. 2002;145(1):76-82.

208. Zijdewind I, Butler JE, Gandevia SC, Taylor JL. The origin of activity in the biceps brachii muscle during voluntary contractions of the contralateral elbow flexor muscles. Experimental brain research. 2006;175(3):526-35.

209. Mayston MJ, Harrison LM, Stephens JA. A neurophysiological study of mirror movements in adults and children. Annals of neurology. 1999;45(5):583-94.

210. Todor JI, Lazarus JA. Exertion level and the intensity of associated movements. Developmental medicine and child neurology. 1986;28(2):205-12.

211. Sehm B, Perez MA, Xu B, Hidler J, Cohen LG. Functional neuroanatomy of mirroring during a unimanual force generation task. Cerebral cortex (New York, NY : 1991). 2010;20(1):34-45.

212. Carson RG. Neural pathways mediating bilateral interactions between the upper limbs. Brain research Brain research reviews. 2005;49(3):641-62.

213. Beaule V, Tremblay S, Theoret H. Interhemispheric control of unilateral movement. Neural plasticity. 2012;2012:627816.

214. Cincotta M, Borgheresi A, Balestrieri F, Giovannelli F, Rossi S, Ragazzoni A, et al. Involvement of the human dorsal premotor cortex in unimanual motor control: an interference approach using transcranial magnetic stimulation. Neuroscience letters. 2004;367(2):189-93.

215. Giovannelli F, Borgheresi A, Balestrieri F, Ragazzoni A, Zaccara G, Cincotta M, et al. Role of the right dorsal premotor cortex in "physiological" mirror EMG activity. Experimental brain research. 2006;175(4):633-40.

216. Maudrich T, Kenville R, Lepsien J, Villringer A, Ragert P. Structural Neural Correlates of Physiological Mirror Activity During Isometric Contractions of Non-Dominant Hand Muscles. Scientific reports. 2018;8(1):9178.

217. Taylor JL, Amann M, Duchateau J, Meeusen R, Rice CL. Neural Contributions to Muscle Fatigue: From the Brain to the Muscle and Back Again. Medicine and science in sports and exercise. 2016;48(11):2294-306.

218. Carroll TJ, Taylor JL, Gandevia SC. Recovery of central and peripheral neuromuscular fatigue after exercise. Journal of applied physiology (Bethesda, Md : 1985). 2017;122(5):1068-76.

219. Nuzzo JL, Taylor JL, Gandevia SC. CORP: Measurement of upper and lower limb muscle strength and voluntary activation. Journal of applied physiology (Bethesda, Md : 1985). 2019;126(3):513-43.

220. Gandevia SC, Allen GM, Butler JE, Taylor JL. Supraspinal factors in human muscle fatigue: evidence for suboptimal output from the motor cortex. The Journal of physiology. 1996;490 (Pt 2):529-36.

221. Taylor JL, Todd G, Gandevia SC. Evidence for a supraspinal contribution to human muscle fatigue. Clin Exp Pharmacol Physiol. 2006;33(4):400-5.

222. Bigland-Ritchie B, Johansson R, Lippold OC, Woods JJ. Contractile speed and EMG changes during fatigue of sustained maximal voluntary contractions. Journal of neurophysiology. 1983;50(1):313-24.

223. Bigland-Ritchie B, Johansson R, Lippold OC, Smith S, Woods JJ. Changes in motoneurone firing rates during sustained maximal voluntary contractions. The Journal of physiology. 1983;340:335-46.

224. Butler JE, Taylor JL, Gandevia SC. Responses of human motoneurons to corticospinal stimulation during maximal voluntary contractions and ischemia. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2003;23(32):10224-30.

225. Duchateau J, Hainaut K. Behaviour of short and long latency reflexes in fatigued human muscles. The Journal of physiology. 1993;471:787-99.

226. Taylor JL, Butler JE, Allen GM, Gandevia SC. Changes in motor cortical excitability during human muscle fatigue. The Journal of physiology. 1996;490 (Pt 2):519-28.

227. Taylor JL, Butler JE, Gandevia SC. Altered responses of human elbow flexors to peripheral-nerve and cortical stimulation during a sustained maximal voluntary contraction. Experimental brain research. 1999;127(1):108-15.

228. Mills KR, Thomson CC. Human muscle fatigue investigated by transcranial magnetic stimulation. Neuroreport. 1995;6(15):1966-8.

229. Hunter SK, Butler JE, Todd G, Gandevia SC, Taylor JL. Supraspinal fatigue does not explain the sex difference in muscle fatigue of maximal contractions. Journal of applied physiology (Bethesda, Md : 1985). 2006;101(4):1036-44.

230. Taylor JL, Allen GM, Butler JE, Gandevia SC. Supraspinal fatigue during intermittent maximal voluntary contractions of the human elbow flexors. Journal of applied physiology (Bethesda, Md : 1985). 2000;89(1):305-13.

231. Hunter SK, Todd G, Butler JE, Gandevia SC, Taylor JL. Recovery from supraspinal fatigue is slowed in old adults after fatiguing maximal isometric contractions. Journal of applied physiology (Bethesda, Md : 1985). 2008;105(4):1199-209.

232. Kennedy DS, McNeil CJ, Gandevia SC, Taylor JL. Firing of antagonist small-diameter muscle afferents reduces voluntary activation and torque of elbow flexors. The Journal of physiology. 2013;591(14):3591-604.

233. Woods JJ, Furbush F, Bigland-Ritchie B. Evidence for a fatigue-induced reflex inhibition of motoneuron firing rates. Journal of neurophysiology. 1987;58(1):125-37.

234. Peters EJ, Fuglevand AJ. Cessation of human motor unit discharge during sustained maximal voluntary contraction. Neuroscience letters. 1999;274(1):66-70.

235. Muddle TWD, Colquhoun RJ, Magrini MA, Luera MJ, DeFreitas JM, Jenkins NDM. Effects of fatiguing, submaximal high- versus low-torque isometric exercise on motor unit recruitment and firing behavior. Physiol Rep. 2018;6(8):e13675.

236. Adam A, De Luca CJ. Firing rates of motor units in human vastus lateralis muscle during fatiguing isometric contractions. Journal of applied physiology (Bethesda, Md : 1985). 2005;99(1):268-80.

237. Carpentier A, Duchateau J, Hainaut K. Motor unit behaviour and contractile changes during fatigue in the human first dorsal interosseus. The Journal of physiology. 2001;534(Pt 3):903-12.

238. Kelly LA, Racinais S, Cresswell AG. Discharge properties of abductor hallucis before, during, and after an isometric fatigue task. Journal of neurophysiology. 2013;110(4):891-8.

239. McNeil CJ, Giesebrecht S, Gandevia SC, Taylor JL. Behaviour of the motoneurone pool in a fatiguing submaximal contraction. The Journal of physiology. 2011;589(Pt 14):3533-44.

240. Søgaard K, Gandevia SC, Todd G, Petersen NT, Taylor JL. The effect of sustained low-intensity contractions on supraspinal fatigue in human elbow flexor muscles. The Journal of physiology. 2006;573(Pt 2):511-23.

241. Klass M, Lévénez M, Enoka RM, Duchateau J. Spinal mechanisms contribute to differences in the time to failure of submaximal fatiguing contractions performed with different loads. Journal of neurophysiology. 2008;99(3):1096-104.

242. van Duinen H, Renken R, Maurits N, Zijdewind I. Effects of motor fatigue on human brain activity, an fMRI study. NeuroImage. 2007;35(4):1438-49.

243. Post M, Bayrak S, Kernell D, Zijdewind I. Contralateral muscle activity and fatigue in the human first dorsal interosseous muscle. Journal of applied physiology (Bethesda, Md : 1985). 2008;105(1):70-82.

244. Muellbacher W, Ziemann U, Boroojerdi B, Cohen L, Hallett M. Role of the human motor cortex in rapid motor learning. Experimental brain research. 2001;136(4):431-8.

245. Classen J, Liepert J, Wise SP, Hallett M, Cohen LG. Rapid plasticity of human cortical movement representation induced by practice. Journal of neurophysiology. 1998;79(2):1117-23.

246. Rioult-Pedotti MS, Friedman D, Hess G, Donoghue JP. Strengthening of horizontal cortical connections following skill learning. Nature neuroscience. 1998;1(3):230-4.

247. Rioult-Pedotti MS, Friedman D, Donoghue JP. Learning-induced LTP in neocortex. Science. 2000;290(5491):533-6.

248. Hallett M. Transcranial magnetic stimulation: a primer. Neuron. 2007;55(2):187-99.

249. Lotze M, Braun C, Birbaumer N, Anders S, Cohen LG. Motor learning elicited by voluntary drive. Brain : a journal of neurology. 2003;126(Pt 4):866-72.

250. Elbert T, Pantev C, Wienbruch C, Rockstroh B, Taub E. Increased cortical representation of the fingers of the left hand in string players. Science. 1995;270(5234):305-7.

251. Cirillo J, Todd G, Semmler JG. Corticomotor excitability and plasticity following complex visuomotor training in young and old adults. The European journal of neuroscience. 2011;34(11):1847-56.

252. Moritani T, deVries HA. Neural factors versus hypertrophy in the time course of muscle strength gain. American journal of physical medicine. 1979;58(3):115-30.

253. Kamen G, Knight CA. Training-related adaptations in motor unit discharge rate in young and older adults. The journals of gerontology Series A, Biological sciences and medical sciences. 2004;59(12):1334-8.

254. Gabriel DA, Kamen G, Frost G. Neural adaptations to resistive exercise: mechanisms and recommendations for training practices. Sports medicine (Auckland, NZ). 2006;36(2):133-49.

255. Del Vecchio A, Casolo A, Negro F, Scorcelletti M, Bazzucchi I, Enoka R, et al. The increase in muscle force after 4 weeks of strength training is mediated by adaptations in motor unit recruitment and rate coding. The Journal of physiology. 2019;597(7):1873-87.

256. Carroll TJ, Riek S, Carson RG. Neural adaptations to resistance training: implications for movement control. Sports medicine (Auckland, NZ). 2001;31(12):829-40.

257. Nuzzo JL, Barry BK, Gandevia SC, Taylor JL. Effects of acute isometric resistance exercise on cervicomedullary motor evoked potentials. Scandinavian journal of medicine & science in sports. 2018.

258. Mason J, Howatson G, Frazer AK, Pearce AJ, Jaberzadeh S, Avela J, et al. Modulation of intracortical inhibition and excitation in agonist and antagonist muscles following acute strength training. European journal of applied physiology. 2019;119(10):2185-99.

259. Mason J, Frazer AK, Jaberzadeh S, Ahtiainen JP, Avela J, Rantalainen T, et al. Determining the Corticospinal Responses to Single Bouts of Skill and Strength Training. Journal of strength and conditioning research. 2019;33(9):2299-307.

260. Latella C, Teo WP, Harris D, Major B, VanderWesthuizen D, Hendy AM. Effects of acute resistance training modality on corticospinal excitability, intra-cortical and neuromuscular responses. European journal of applied physiology. 2017;117(11):2211-24.

261. Latella C, Hendy AM, Pearce AJ, VanderWesthuizen D, Teo WP. The Time-Course of Acute Changes in Corticospinal Excitability, Intra-Cortical Inhibition and Facilitation Following a Single-Session Heavy Strength Training of the Biceps Brachii. Frontiers in human neuroscience. 2016;10:607.

262. Latella C, Goodwill AM, Muthalib M, Hendy AM, Major B, Nosaka K, et al. Effects of eccentric versus concentric contractions of the biceps brachii on intracortical inhibition and facilitation. Scandinavian journal of medicine & science in sports. 2019;29(3):369-79.

263. Brandner CR, Warmington SA, Kidgell DJ. Corticomotor Excitability is Increased Following an Acute Bout of Blood Flow Restriction Resistance Exercise. Frontiers in human neuroscience. 2015;9:652.

264. Ruotsalainen I, Ahtiainen JP, Kidgell DJ, Avela J. Changes in corticospinal excitability during an acute bout of resistance exercise in the elbow flexors. European journal of applied physiology. 2014;114(7):1545-53.

265. Mason J, Frazer A, Pearce A, Goodwill A, Jaberzadeh S, Howatson G, et al. Determining the early corticospinal-motoneuronal responses to strength training: A systematic review and meta-analysis2018.

266. Gruber M, Linnamo V, Strojnik V, Rantalainen T, Avela J. Excitability at the motoneuron pool and motor cortex is specifically modulated in lengthening compared to isometric contractions. Journal of neurophysiology. 2009;101(4):2030-40.

267. Coco M, Alagona G, Rapisarda G, Costanzo E, Calogero RA, Perciavalle V, et al. Elevated blood lactate is associated with increased motor cortex excitability. Somatosensory & motor research. 2010;27(1):1-8.

268. Hortobágyi T, Barrier J, Beard D, Braspennincx J, Koens P, Devita P, et al. Greater initial adaptations to submaximal muscle lengthening than maximal shortening. Journal of applied physiology (Bethesda, Md : 1985). 1996;81(4):1677-82.

269. Coyle EF, Feiring DC, Rotkis TC, Cote RW, 3rd, Roby FB, Lee W, et al. Specificity of power improvements through slow and fast isokinetic training.

Journal of applied physiology: respiratory, environmental and exercise physiology. 1981;51(6):1437-42.

270. Baker D, Wilson G, Carlyon B. Generality versus specificity: A comparison of dynamic and isometric measures of strength and speed-strength. European journal of applied physiology and occupational physiology. 1994;68:350-5.

271. Cormie P, McGuigan MR, Newton RU. Developing maximal neuromuscular power: Part 1--biological basis of maximal power production. Sports medicine (Auckland, NZ). 2011;41(1):17-38.

272. Moss BM, Refsnes PE, Abildgaard A, Nicolaysen K, Jensen J. Effects of maximal effort strength training with different loads on dynamic strength, cross-sectional area, load-power and load-velocity relationships. European journal of applied physiology and occupational physiology. 1997;75(3):193-9.

273. Häkkinen K, Komi PV, Alén M. Effect of explosive type strength training on isometric force- and relaxation-time, electromyographic and muscle fibre characteristics of leg extensor muscles. Acta physiologica Scandinavica. 1985;125(4):587-600.

274. Behm DG, Sale DG. Intended rather than actual movement velocity determines velocity-specific training response. Journal of applied physiology (Bethesda, Md : 1985). 1993;74(1):359-68.

275. Reid KF, Fielding RA. Skeletal muscle power: a critical determinant of physical functioning in older adults. Exercise and sport sciences reviews. 2012;40(1):4-12.

276. Schoenfeld B. Science and development of muscle hypertrophy2016.

277. Beneke R, Neuerburg J, Bohndorf K. Muscle cross-section measurement by magnetic resonance imaging. European journal of applied physiology and occupational physiology. 1991;63(6):424-9.

278. Cramer J, Palmer I, Ryan E, Herda T, Bemben D, Bemben M, et al. Validity and Reliability of a Peripheral Quantitative Computed Tomography Scanner for Measuring Muscle Cross-sectional Area: 1496. Medicine and Science in Sports and Exercise - MED SCI SPORT EXERCISE. 2007;39.

279. DeFreitas JM, Beck TW, Stock MS, Dillon MA, Sherk VD, Stout JR, et al. A comparison of techniques for estimating training-induced changes in muscle cross-sectional area. Journal of strength and conditioning research / National Strength & Conditioning Association. 2010;24(9):2383-9.

280. Housh DJ, Housh TJ, Weir JP, Weir LL, Johnson GO, Stout JR. Anthropometric estimation of thigh muscle cross-sectional area. Medicine and science in sports and exercise. 1995;27(5):784-91.

281. Young A, Stokes M, Round JM, Edwards RH. The effect of high-resistance training on the strength and cross-sectional area of the human quadriceps. European journal of clinical investigation. 1983;13(5):411-7.

282. Seynnes OR, de Boer M, Narici MV. Early skeletal muscle hypertrophy and architectural changes in response to high-intensity resistance training. Journal of applied physiology (Bethesda, Md : 1985). 2007;102(1):368-73.

283. Phillips SM. Short-term training: when do repeated bouts of resistance exercise become training? Canadian journal of applied physiology = Revue canadienne de physiologie appliquee. 2000;25(3):185-93.

284. Loenneke JP, Rossow LM, Fahs CA, Thiebaud RS, Grant Mouser J, Bemben MG. Time-course of muscle growth, and its relationship with muscle strength in both young and older women. Geriatrics & gerontology international. 2017;17(11):2000-7.

285. DeFreitas JM, Beck TW, Stock MS, Dillon MA, Kasishke PR, 2nd. An examination of the time course of training-induced skeletal muscle hypertrophy. European journal of applied physiology. 2011;111(11):2785-90.

286. Hubal MJ, Gordish-Dressman H, Thompson PD, Price TB, Hoffman EP, Angelopoulos TJ, et al. Variability in muscle size and strength gain after unilateral resistance training. Medicine and science in sports and exercise. 2005;37(6):964-72.

287. Pescatello LS, Devaney JM, Hubal MJ, Thompson PD, Hoffman EP. Highlights from the functional single nucleotide polymorphisms associated with human muscle size and strength or FAMuSS study. Biomed Res Int. 2013;2013:643575.

288. Lemmer JT, Hurlbut DE, Martel GF, Tracy BL, Ivey FM, Metter EJ, et al. Age and gender responses to strength training and detraining. Medicine and science in sports and exercise. 2000;32(8):1505-12.

289. Ahtiainen JP, Pakarinen A, Alen M, Kraemer WJ, Häkkinen K. Muscle hypertrophy, hormonal adaptations and strength development during strength training in strength-trained and untrained men. European journal of applied physiology. 2003;89(6):555-63.

290. Szeto G, Strauss GR, Domenico GD, Lai HS. The effect of training intensity on voluntary isometric strength improvement. The Australian journal of physiotherapy. 1989;35(4):210-7.

291. Schott J, McCully K, Rutherford OM. The role of metabolites in strength training. II. Short versus long isometric contractions. European journal of applied physiology and occupational physiology. 1995;71(4):337-41.

292. Schoenfeld BJ, Ogborn D, Krieger JW. Dose-response relationship between weekly resistance training volume and increases in muscle mass: A systematic review and meta-analysis. Journal of sports sciences. 2017;35(11):1073-82.

293. Figueiredo VC, de Salles BF, Trajano GS. Volume for Muscle Hypertrophy and Health Outcomes: The Most Effective Variable in Resistance Training. Sports medicine (Auckland, NZ). 2017.

294. Šarić J, Lisica D, Orlić I, Grgic J, Krieger J, Vuk S, et al. Resistance training frequencies of 3 and 6 times per week produce similar muscular adaptations in resistance-trained men2018.

295. Dankel SJ, Mattocks KT, Jessee MB, Buckner SL, Mouser JG, Counts BR, et al. Frequency: The Overlooked Resistance Training Variable for Inducing Muscle Hypertrophy? Sports medicine (Auckland, NZ). 2017;47(5):799-805.

296. Oranchuk DJ, Storey AG, Nelson AR, Cronin JB. Isometric training and long-term adaptations: Effects of muscle length, intensity, and intent: A systematic review. Scandinavian journal of medicine & science in sports. 2019;29(4):484-503.

297. Schoenfeld BJ, Ogborn DI, Vigotsky AD, Franchi MV, Krieger JW. Hypertrophic Effects of Concentric vs. Eccentric Muscle Actions: A Systematic Review and Meta-analysis. Journal of strength and conditioning research / National Strength & Conditioning Association. 2017;31(9):2599-608.

298. Roig M, O'Brien K, Kirk G, Murray R, McKinnon P, Shadgan B, et al. The effects of eccentric versus concentric resistance training on muscle strength

and mass in healthy adults: a systematic review with meta-analysis. British journal of sports medicine. 2009;43(8):556-68.

299. Aagaard P, Simonsen EB, Andersen JL, Magnusson SP, Halkjaer-Kristensen J, Dyhre-Poulsen P. Neural inhibition during maximal eccentric and concentric quadriceps contraction: effects of resistance training. Journal of applied physiology (Bethesda, Md : 1985). 2000;89(6):2249-57.

300. Hortobágyi T, Hill JP, Houmard JA, Fraser DD, Lambert NJ, Israel RG. Adaptive responses to muscle lengthening and shortening in humans. Journal of applied physiology (Bethesda, Md : 1985). 1996;80(3):765-72.

301. TAN B. Manipulating Resistance Training Program Variables to Optimize Maximum Strength in Men: A Review. The Journal of Strength & Conditioning Research. 1999;13(3):289-304.

302. Morton RW, Sonne MW, Farias Zuniga A, Mohammad IYZ, Jones A, McGlory C, et al. Muscle fibre activation is unaffected by load and repetition duration when resistance exercise is performed to task failure. The Journal of physiology. 2019;597(17):4601-13.

303. Sánchez-Medina L, González-Badillo JJ. Velocity loss as an indicator of neuromuscular fatigue during resistance training. Medicine and science in sports and exercise. 2011;43(9):1725-34.

304. González-Badillo JJ, Marques MC, Sánchez-Medina L. The importance of movement velocity as a measure to control resistance training intensity. Journal of human kinetics. 2011;29a:15-9.

305. Balsalobre-Fernández C, Muñoz López M, Marchante D, García Ramos A. Repetitions in Reserve and Rate of Perceived Exertion Increase the Prediction Capabilities of the Load-Velocity Relationship2018.

306. Morán-Navarro R, Martínez-Cava A, Sánchez-Medina L, Mora-Rodríguez R, González-Badillo JJ, Pallarés JG. Movement Velocity as a Measure of Level of Effort During Resistance Exercise. Journal of strength and conditioning research / National Strength & Conditioning Association. 2019;33(6):1496-504.

307. Pareja-Blanco F, Rodriguez-Rosell D, Sanchez-Medina L, Ribas-Serna J, Lopez-Lopez C, Mora-Custodio R, et al. Acute and delayed response to resistance exercise leading or not leading to muscle failure. Clinical physiology and functional imaging. 2016.

308. Haff GG, Whitley A, McCoy LB, O'Bryant HS, Kilgore JL, Haff EE, et al. Effects of different set configurations on barbell velocity and displacement during a clean pull. Journal of strength and conditioning research / National Strength & Conditioning Association. 2003;17(1):95-103.

309. Haff GG, Hobbs RT, Haff EE, Sands WA, Pierce KC, Stone MH. Cluster Training: A Novel Method for Introducing Training Program Variation. Strength & Conditioning Journal. 2008;30(1):67-76.

310. Smith RC, Rutherford OM. The role of metabolites in strength training. I. A comparison of eccentric and concentric contractions. European journal of applied physiology and occupational physiology. 1995;71(4):332-6.

311. Willardson JM. The application of training to failure in periodized multiple-set resistance exercise programs. Journal of strength and conditioning research / National Strength & Conditioning Association. 2007;21(2):628-31.

312. Willardson JM, Norton L, Wilson G. Training to Failure and Beyond in Mainstream Resistance Exercise Programs. Strength & Conditioning Journal. 2010;32(3):21-9.

313. Takarada Y, Takazawa H, Sato Y, Takebayashi S, Tanaka Y, Ishii N. Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans. Journal of applied physiology (Bethesda, Md : 1985). 2000;88(6):2097-106.

314. Burd NA, West DW, Staples AW, Atherton PJ, Baker JM, Moore DR, et al. Low-load high volume resistance exercise stimulates muscle protein synthesis more than high-load low volume resistance exercise in young men. PloS one. 2010;5(8):e12033.

315. Burd NA, Mitchell CJ, Churchward-Venne TA, Phillips SM. Bigger weights may not beget bigger muscles: evidence from acute muscle protein synthetic responses after resistance exercise. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme. 2012;37(3):551-4.

316. Nóbrega SR, Libardi CA. Is Resistance Training to Muscular Failure Necessary? Front Physiol. 2016;7:10.

317. Kannus P, Alosa D, Cook L, Johnson RJ, Renstrom P, Pope M, et al. Effect of one-legged exercise on the strength, power and endurance of the contralateral leg. A randomized, controlled study using isometric and concentric

isokinetic training. European journal of applied physiology and occupational physiology. 1992;64(2):117-26.

318. Andrushko JW, Gould LA, Farthing JP. Contralateral effects of unilateral training: sparing of muscle strength and size after immobilization. Applied Physiology, Nutrition, and Metabolism. 2018;43(11):1131-9.

319. Lepley LK, Grooms DR, Burland JP, Davi SM, Mosher JL, Cormier ML, et al. Eccentric cross-exercise after anterior cruciate ligament reconstruction: Novel case series to enhance neuroplasticity. Physical Therapy in Sport. 2018;34:55-65.

320. Farthing JP, Chilibeck PD. The effect of eccentric training at different velocities on cross-education. European journal of applied physiology. 2003;89(6):570-7.

321. Narici MV, Roi GS, Landoni L, Minetti AE, Cerretelli P. Changes in force, cross-sectional area and neural activation during strength training and detraining of the human quadriceps. European journal of applied physiology and occupational physiology. 1989;59(4):310-9.

322. Cannon RJ, Cafarelli E. Neuromuscular adaptations to training. Journal of applied physiology (Bethesda, Md : 1985). 1987;63(6):2396-402.

323. Farthing JP, Chilibeck PD, Binsted G. Cross-education of arm muscular strength is unidirectional in right-handed individuals. Medicine and science in sports and exercise. 2005;37(9):1594-600.

324. Adamson M, Macquaide N, Helgerud J, Hoff J, Kemi OJ. Unilateral arm strength training improves contralateral peak force and rate of force development. European journal of applied physiology. 2008;103(5):553-9.

325. Hortobagyi T, Richardson SP, Lomarev M, Shamim E, Meunier S, Russman H, et al. Interhemispheric plasticity in humans. Medicine and science in sports and exercise. 2011;43(7):1188-99.

326. Lagerquist O, Zehr EP, Docherty D. Increased spinal reflex excitability is not associated with neural plasticity underlying the cross-education effect. Journal of applied physiology (Bethesda, Md : 1985). 2006;100(1):83-90.

327. Coombs TA, Frazer AK, Horvath DM, Pearce AJ, Howatson G, Kidgell DJ. Cross-education of wrist extensor strength is not influenced by non-dominant training in right-handers. European journal of applied physiology. 2016;116(9):1757-69.

328. Abazović E, Kovačević E, Kovac S, Bradić J. The effect of training of the non-dominant knee muscles on ipsi- and contralateral strength gains. Isokinetics and exercise science. 2015;23:177-82.

329. Ward NS. Compensatory mechanisms in the aging motor system. Ageing research reviews. 2006;5(3):239-54.

330. Hester GM, Magrini MA, Colquhoun RJ, Barrera-Curiel A, Estrada CA, Olmos AA, et al. Cross-education: effects of age on rapid and maximal voluntary contractile characteristics in males. European journal of applied physiology. 2019.

331. Tracy BL, Ivey FM, Hurlbut D, Martel GF, Lemmer JT, Siegel EL, et al. Muscle quality. II. Effects Of strength training in 65- to 75-yr-old men and women. Journal of applied physiology (Bethesda, Md : 1985). 1999;86(1):195-201.

332. Manca A, Ginatempo F, Cabboi MP, Mercante B, Ortu E, Dragone D, et al. No evidence of neural adaptations following chronic unilateral isometric training of the intrinsic muscles of the hand: a randomized controlled study. European journal of applied physiology. 2016;116(10):1993-2005.

333. Weir JP, Housh TJ, Weir LL. Electromyographic evaluation of joint angle specificity and cross-training after isometric training. Journal of applied physiology (Bethesda, Md : 1985). 1994;77(1):197-201.

334. Housh TJ, Housh DJ, Weir JP, Weir LL. Effects of eccentric-only resistance training and detraining. International journal of sports medicine. 1996;17(2):145-8.

335. Goodwill AM, Pearce AJ, Kidgell DJ. Corticomotor plasticity following unilateral strength training. Muscle & nerve. 2012;46(3):384-93.

336. Leung M, Rantalainen T, Teo WP, Kidgell D. The ipsilateral corticospinal responses to cross-education are dependent upon the motor-training intervention. Experimental brain research. 2018.

337. Mason J, Frazer AK, Horvath DM, Pearce AJ, Avela J, Howatson G, et al. Ipsilateral corticomotor responses are confined to the homologous muscle following cross-education of muscular strength. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme. 2017;43(1):11-22.

338. Sun Y, Ledwell NMH, Boyd LA, Zehr EP. Unilateral wrist extension training after stroke improves strength and neural plasticity in both arms. Experimental brain research. 2018;236(7):2009-21.

339. Barss TS, Klarner T, Pearcey GEP, Sun Y, Zehr EP. Time course of interlimb strength transfer after unilateral handgrip training. Journal of Applied Physiology. 2018;125(5):1594-608.

340. Young K, McDonagh MJN, Davies CTM. The effects of two forms of isometric training on the mechanical properties of the triceps surae in man. Pflügers Archiv. 1985;405(4):384-8.

341. Magnus CR, Boychuk K, Kim SY, Farthing JP. At-home resistance tubing strength training increases shoulder strength in the trained and untrained limb. Scandinavian journal of medicine & science in sports. 2014;24(3):586-93.

342. Fariñas J, Mayo X, Giráldez García M, Carballeira E, Fernández-Del-Olmo M, Rial-Vázquez J, et al. Set Configuration in Strength Training Programs Modulates the Cross Education Phenomenon. The Journal of Strength and Conditioning Research. 2019;Online ahead of print.

343. García Ramos A, Nebot V, Padial P, Valverde T, Pablos-Monzó A, Feriche B. Effects of short inter-repetition rest periods on power output losses during the half squat exercise. Isokinetics and exercise science. 2016;24(4):323-30.

344. Aagaard P. Training-induced changes in neural function. Exercise and sport sciences reviews. 2003;31(2):61-7.

345. Duchateau J, Semmler JG, Enoka RM. Training adaptations in the behavior of human motor units. Journal of applied physiology (Bethesda, Md : 1985). 2006;101(6):1766-75.

346. Farina D, Merletti R, Enoka RM. The extraction of neural strategies from the surface EMG: an update. Journal of applied physiology (Bethesda, Md : 1985). 2014;117(11):1215-30.

347. Higbie EJ, Cureton KJ, Warren GL, 3rd, Prior BM. Effects of concentric and eccentric training on muscle strength, cross-sectional area, and neural activation. Journal of applied physiology (Bethesda, Md : 1985). 1996;81(5):2173-81.

348. Häkkinen K, Newton RU, Gordon SE, McCormick M, Volek JS, Nindl BC, et al. Changes in muscle morphology, electromyographic activity, and force production characteristics during progressive strength training in young

and older men. The journals of gerontology Series A, Biological sciences and medical sciences. 1998;53(6):B415-23.

349. Häkkinen K, Komi PV. Training-induced changes in neuromuscular performance under voluntary and reflex conditions. European journal of applied physiology and occupational physiology. 1986;55(2):147-55.

350. Häkkinen K, Komi PV. Electromyographic changes during strength training and detraining. Medicine and science in sports and exercise. 1983;15(6):455-60.

351. Häkkinen K, Kallinen M, Izquierdo M, Jokelainen K, Lassila H, Mälkiä E, et al. Changes in agonist-antagonist EMG, muscle CSA, and force during strength training in middle-aged and older people. Journal of applied physiology (Bethesda, Md : 1985). 1998;84(4):1341-9.

352. Häkkinen K, Alén M, Komi PV. Changes in isometric force- and relaxation-time, electromyographic and muscle fibre characteristics of human skeletal muscle during strength training and detraining. Acta physiologica Scandinavica. 1985;125(4):573-85.

353. Andersen LL, Andersen JL, Magnusson SP, Aagaard P. Neuromuscular adaptations to detraining following resistance training in previously untrained subjects. European journal of applied physiology. 2005;93(5-6):511-8.

354. Balshaw TG, Massey GJ, Maden-Wilkinson TM, Morales-Artacho AJ, McKeown A, Appleby CL, et al. Changes in agonist neural drive, hypertrophy and pre-training strength all contribute to the individual strength gains after resistance training. European journal of applied physiology. 2017;117(4):631-40.

355. Balshaw TG, Massey GJ, Maden-Wilkinson TM, Lanza MB, Folland JP. Neural adaptations after 4 years vs. 12 weeks of resistance training vs. untrained. Scandinavian journal of medicine & science in sports. 2019;29(3).

356. Carolan B, Cafarelli E. Adaptations in coactivation after isometric resistance training. Journal of applied physiology (Bethesda, Md : 1985). 1992;73(3):911-7.

357. Farina D. Interpretation of the surface electromyogram in dynamic contractions. Exercise and sport sciences reviews. 2006;34(3):121-7.

358. Arabadzhiev TI, Dimitrov VG, Dimitrov GV. The increase in surface EMG could be a misleading measure of neural adaptation during the

early gains in strength. European journal of applied physiology. 2014;114(8):1645-55.

359. Herbert RD, Dean C, Gandevia SC. Effects of real and imagined training on voluntary muscle activation during maximal isometric contractions. Acta physiologica Scandinavica. 1998;163(4):361-8.

360. Taylor JL. Point: the interpolated twitch does/does not provide a valid measure of the voluntary activation of muscle. Journal of applied physiology (Bethesda, Md : 1985). 2009;107(1):354-5.

361. Brown AB, McCartney N, Sale DG. Positive adaptations to weight-lifting training in the elderly. Journal of applied physiology (Bethesda, Md : 1985). 1990;69(5):1725-33.

362. Giboin LS, Weiss B, Thomas F, Gruber M. Neuroplasticity following short-term strength training occurs at supraspinal level and is specific for the trained task. Acta physiologica (Oxford, England). 2018;222(4):e12998.

363. Hvid LG, Strotmeyer ES, Skjødt M, Magnussen LV, Andersen M, Caserotti P. Voluntary muscle activation improves with power training and is associated with changes in gait speed in mobility-limited older adults - A randomized controlled trial. Experimental gerontology. 2016;80:51-6.

364. Scaglioni G, Ferri A, Minetti AE, Martin A, Van Hoecke J, Capodaglio P, et al. Plantar flexor activation capacity and H reflex in older adults: adaptations to strength training. Journal of applied physiology (Bethesda, Md : 1985). 2002;92(6):2292-302.

365. Pucci AR, Griffin L, Cafarelli E. Maximal motor unit firing rates during isometric resistance training in men. Experimental physiology. 2006;91(1):171-8.

366. Pensini M, Martin A, Maffiuletti NA. Central versus peripheral adaptations following eccentric resistance training. International journal of sports medicine. 2002;23(8):567-74.

367. Brown N, Bubeck D, Haeufle DFB, Weickenmeier J, Kuhl E, Alt W, et al. Weekly Time Course of Neuro-Muscular Adaptation to Intensive Strength Training. Front Physiol. 2017;8:329.

368. Behrens M, Mau-Moeller A, Mueller K, Heise S, Gube M, Beuster N, et al. Plyometric training improves voluntary activation and strength during

isometric, concentric and eccentric contractions. Journal of science and medicine in sport / Sports Medicine Australia. 2016;19(2):170-6.

369. Vila-Cha C, Falla D, Farina D. Motor unit behavior during submaximal contractions following six weeks of either endurance or strength training. Journal of applied physiology (Bethesda, Md : 1985). 2010;109(5):1455-66.

370. Christie A, Kamen G. Short-term training adaptations in maximal motor unit firing rates and afterhyperpolarization duration. Muscle & nerve. 2010;41(5):651-60.

371. Kim EH, Hassan AS, Heckman CJ. Changes in motor unit discharge patterns following strength training. The Journal of physiology. 2019;597(14):3509-10.

372. Fimland MS, Helgerud J, Gruber M, Leivseth G, Hoff J. Functional maximal strength training induces neural transfer to single-joint tasks. European journal of applied physiology. 2009;107(1):21-9.

373. Gardiner P, Dai Y, Heckman CJ. Effects of exercise training on alpha-motoneurons. Journal of applied physiology (Bethesda, Md : 1985). 2006;101(4):1228-36.

374. Jacobs BL, Martín-Cora FJ, Fornal CA. Activity of medullary serotonergic neurons in freely moving animals. Brain research Brain research reviews. 2002;40(1-3):45-52.

375. Macefield VG, Gandevia SC, Bigland-Ritchie B, Gorman RB, Burke D. The firing rates of human motoneurones voluntarily activated in the absence of muscle afferent feedback. The Journal of physiology. 1993;471:429-43.

376. Weier AT, Kidgell DJ. Strength training with superimposed whole body vibration does not preferentially modulate cortical plasticity. TheScientificWorldJournal. 2012;2012:876328.

377. Leung M, Spittle M, Kidgell D. Corticospinal Excitability Following Short-Term Motor Imagery Training of a Strength Task. Journal of Imagery Research in Sport and Physical Activity. 2013;8.

378. Palmer HS, Haberg AK, Fimland MS, Solstad GM, Moe Iversen V, Hoff J, et al. Structural brain changes after 4 wk of unilateral strength training of the lower limb. Journal of applied physiology (Bethesda, Md : 1985). 2013;115(2):167-75.

379. Lee M, Gandevia SC, Carroll TJ. Unilateral strength training increases voluntary activation of the opposite untrained limb. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2009;120(4):802-8.

380. Colomer-Poveda D, Romero-Arenas S, Hortobagyi T, Marquez G. Does ipsilateral corticospinal excitability play a decisive role in the cross-education effect caused by unilateral resistance training? A systematic review. Neurologia (Barcelona, Spain). 2018.

381. Martin A, Haxby JV, Lalonde FM, Wiggs CL, Ungerleider LG. Discrete cortical regions associated with knowledge of color and knowledge of action. Science. 1995;270(5233):102-5.

382. Perez MA, Lungholt BK, Nyborg K, Nielsen JB. Motor skill training induces changes in the excitability of the leg cortical area in healthy humans. Experimental brain research. 2004;159(2):197-205.

383. Ruotsalainen I, Ahtiainen JP, Kidgell DJ, Avela J. Changes in corticospinal excitability during an acute bout of resistance exercise in the elbow flexors. European journal of applied physiology. 2014;114(7):1545-53.

384. Lundbye-Jensen J, Petersen TH, Rothwell JC, Nielsen JB. Interference in ballistic motor learning: specificity and role of sensory error signals. PloS one. 2011;6(3):e17451.

385. Butefisch CM, Davis BC, Wise SP, Sawaki L, Kopylev L, Classen J, et al. Mechanisms of use-dependent plasticity in the human motor cortex. Proceedings of the National Academy of Sciences of the United States of America. 2000;97(7):3661-5.

386. Delvendahl I, Kuhnke NG, Jung NH, Mainberger F, Cronjaeger M, Unterrainer J, et al. The time course of motor cortex plasticity after spaced motor practice. Brain stimulation. 2011;4(3):156-64.

387. Rogasch NC, Dartnall TJ, Cirillo J, Nordstrom MA, Semmler JG. Corticomotor plasticity and learning of a ballistic thumb training task are diminished in older adults. Journal of applied physiology (Bethesda, Md : 1985). 2009;107(6):1874-83.

388. Ziemann U, Muellbacher W, Hallett M, Cohen LG. Modulation of practice-dependent plasticity in human motor cortex. Brain : a journal of neurology. 2001;124(Pt 6):1171-81.

389. Weavil JC, Sidhu SK, Mangum TS, Richardson RS, Amann M. Intensity-dependent alterations in the excitability of cortical and spinal projections to the knee extensors during isometric and locomotor exercise. American journal of physiology Regulatory, integrative and comparative physiology. 2015;308(12):R998-1007.

390. Todd G, Taylor JL, Gandevia SC. Reproducible measurement of voluntary activation of human elbow flexors with motor cortical stimulation. Journal of applied physiology (Bethesda, Md : 1985). 2004;97(1):236-42.

391. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. Journal of Chiropractic Medicine. 2016;15(2):155-63.

392. Cohen J. CHAPTER 8 - F Tests on Means in the Analysis of Variance and Covariance. In: Cohen J, editor. Statistical Power Analysis for the Behavioral Sciences: Academic Press; 1977. p. 273-406.

393. Gandevia SC, Petersen N, Butler JE, Taylor JL. Impaired response of human motoneurones to corticospinal stimulation after voluntary exercise. The Journal of physiology. 1999;521(Pt 3):749-59.

394. Munn J, Herbert RD, Hancock MJ, Gandevia SC. Resistance training for strength: effect of number of sets and contraction speed. Medicine and science in sports and exercise. 2005;37(9):1622-6.

395. Schulze K, Luders E, Jancke L. Intermanual transfer in a simple motor task. Cortex. 2002;38(5):805-15.

396. Perez MA, Tanaka S, Wise SP, Sadato N, Tanabe HC, Willingham DT, et al. Neural substrates of intermanual transfer of a newly acquired motor skill. Curr Biol. 2007;17(21):1896-902.

397. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015;4:1.

398. Harris JD, Quatman CE, Manring MM, Siston RA, Flanigan DC. How to Write a Systematic Review. The American journal of sports medicine. 2014;42(11):2761-8.

399. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Physical therapy. 2003;83(8):713-21.

400. National Heart LaBI, National Institutes of Health. Quality Assessment Tool for Before-after (Pre-post) Studies with No Control Group. 2014;p. 1:2018.

401. Triscott S, Gordon J, Kuppuswamy A, King N, Davey N, Ellaway P. Differential effects of endurance and resistance training on central fatigue. Journal of sports sciences. 2008;26(9):941-51.

402. Goodall S, Gibson AS, Voller B, Lomarev M, Howatson G, Dang N, et al. Repetitive Transcranial Magnetic Stimulation Attenuates the Perception of Force Output Production in Non-Exercised Hand Muscles after Unilateral Exercise. PloS one. 2013;8(11):9.

403. Schmidt MW, Hinder MR, Summers JJ, Garry MI. Long-Lasting Contralateral Motor Cortex Excitability Is Increased by Unilateral Hand Movement That Triggers Electrical Stimulation of Opposite Homologous Muscles. Neurorehabilitation and neural repair. 2011;25(6):521-30.

404. Lagerquist O, Mang CS, Collins DF. Changes in spinal but not cortical excitability following combined electrical stimulation of the tibial nerve and voluntary plantar-flexion. Experimental brain research. 2012;222(1-2):41-53.

405. Humphry AT, Lloyd-Davies EJ, Teare RJ, Williams KE, Strutton PH, Davey NJ. Specificity and functional impact of post-exercise depression of cortically evoked motor potentials in man. European journal of applied physiology. 2004;92(1-2):211-8.

406. Gorsler A, Zittel S, Weiller C, Munchau A, Liepert J. Modulation of motor cortex excitability induced by pinch grip repetition. Journal of neural transmission (Vienna, Austria : 1996). 2004;111(8):1005-16.

407. Takahashi K, Maruyama A, Maeda M, Etoh S, Hirakoba K, Kawahira K, et al. Unilateral grip fatigue reduces short interval intracortical inhibition in ipsilateral primary motor cortex. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2009;120(1):198-203.

408. Edgley SA, Winter AP. Different effects of fatiguing exercise on corticospinal and transcallosal excitability in human hand area motor cortex. Experimental brain research. 2004;159(4):530-6.

409. Baumer T, Munchau A, Weiller C, Lieper J. Fatigue suppresses ipsilateral intracortical facilitation. Experimental brain research. 2002;146(4):467-73.

410. 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. Frontiers in neurology. 2015;6:119.

411. Tallent J, Goodall S, Hortobagyi T, St Clair Gibson A, Howatson G. Corticospinal responses of resistance-trained and un-trained males during dynamic muscle contractions. Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology. 2013;23(5):1075-81.

412. Berghuis KMM, Semmler JG, Opie GM, Post AK, Hortobagyi T. Age-related changes in corticospinal excitability and intracortical inhibition after upper extremity motor learning: a systematic review and meta-analysis. Neurobiology of aging. 2017;55:61-71.

413. Mochizuki H, Huang YZ, Rothwell JC. Interhemispheric interaction between human dorsal premotor and contralateral primary motor cortex. The Journal of physiology. 2004;561(Pt 1):331-8.

414. Koch G, Fernandez Del Olmo M, Cheeran B, Ruge D, Schippling S, Caltagirone C, et al. Focal stimulation of the posterior parietal cortex increases the excitability of the ipsilateral motor cortex. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2007;27(25):6815-22.

415. Griffin JW, Tooms RE, vander Zwaag R, Bertorini TE, O'Toole ML. Eccentric muscle performance of elbow and knee muscle groups in untrained men and women. Medicine and science in sports and exercise. 1993;25(8):936-44.

416. Ackerley SJ, Stinear CM, Byblow WD. The effect of coordination mode on use-dependent plasticity. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2007;118(8):1759-66.

417. Ackerley SJ, Stinear CM, Byblow WD. Promoting use-dependent plasticity with externally-paced training. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2011;122(12):2462-8.

418. Jantzen KJ, Steinberg FL, Kelso JA. Coordination dynamics of large-scale neural circuitry underlying rhythmic sensorimotor behavior. Journal of cognitive neuroscience. 2009;21(12):2420-33.

419. Stinear CM, Byblow WD. Role of intracortical inhibition in selective hand muscle activation. Journal of neurophysiology. 2003;89(4):2014-20.

420. Colomer-Poveda D, Romero-Arenas S, Lundbye-Jensen J, Hortobagyi T, Marquez G. Contraction intensity-dependent variations in the responses to brain and corticospinal tract stimulation after a single session of resistance training in men. Journal of applied physiology (Bethesda, Md : 1985). 2019;127(4):1128-39.

421. Nakamura H, Kitagawa H, Kawaguchi Y, Tsuji H. Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. The Journal of physiology. 1997;498 (Pt 3)(Pt 3):817-23.

422. Kidgell DJ, Bonanno DR, Frazer AK, Howatson G, Pearce AJ. Corticospinal responses following strength training: a systematic review and meta-analysis. The European journal of neuroscience. 2017;46(11):2648-61.

423. Keller A. Intrinsic Synaptic Organization of the Motor Cortex. Cerebral Cortex. 1993;3(5):430-41.

424. Kimberley TJ, Borich MR, Prochaska KD, Mundfrom SL, Perkins AE, Poepping JM. Establishing the definition and inter-rater reliability of cortical silent period calculation in subjects with focal hand dystonia and healthy controls. Neuroscience letters. 2009;464(2):84-7.

425. Daskalakis ZJ, Christensen BK, Fitzgerald PB, Roshan L, Chen R. The mechanisms of interhemispheric inhibition in the human motor cortex. The Journal of physiology. 2002;543(Pt 1):317-26.

426. Pearcey GEP, Power KE, Button DC. Differences in Supraspinal and Spinal Excitability during Various Force Outputs of the Biceps Brachii in Chronic- and Non-Resistance Trained Individuals. PloS one. 2014;9(5):e98468.

427. Lee M, Hinder MR, Gandevia SC, Carroll TJ. The ipsilateral motor cortex contributes to cross-limb transfer of performance gains after ballistic motor practice. The Journal of physiology. 2010;588(Pt 1):201-12.

428. Legrand D, Vaes B, Mathei C, Adriaensen W, Van Pottelbergh G, Degryse JM. Muscle strength and physical performance as predictors of mortality,

hospitalization, and disability in the oldest old. Journal of the American Geriatrics Society. 2014;62(6):1030-8.

429. Lagally KM, Robertson RJ. Construct validity of the OMNI resistance exercise scale. Journal of strength and conditioning research. 2006;20(2):252-6.

430. Morán-Navarro R, Pérez CE, Mora-Rodríguez R, de la Cruz-Sánchez E, González-Badillo JJ, Sánchez-Medina L, et al. Time course of recovery following resistance training leading or not to failure. European journal of applied physiology. 2017;117(12):2387-99.

431. Colomer-Poveda D, Hortobágyi T, Keller M, Romero-Arenas S, Márquez G. Training intensity-dependent increases in corticospinal but not intracortical excitability after acute strength training. Scandinavian journal of medicine & science in sports. 2019:10.1111/sms.13608.

432. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. Journal of strength and conditioning research. 2010;24(10):2857-72.

433. Ansdell P, Brownstein CG, Škarabot J, Angius L, Kidgell D, Frazer A, et al. Task-specific strength increases after lower-limb compound resistance training occurred in the absence of corticospinal changes in vastus lateralis. Experimental physiology. 2020;n/a(n/a).

434. Baker SN, Perez MA. Reticulospinal Contributions to Gross Hand Function after Human Spinal Cord Injury. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2017;37(40):9778-84.

435. Riddle CN, Edgley SA, Baker SN. Direct and indirect connections with upper limb motoneurons from the primate reticulospinal tract. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2009;29(15):4993-9.

436. Colomer-Poveda D, Romero-Arenas S, Fariñas J, Iglesias-Soler E, Hortobagyi T, Marquez G. Training load but not fatigue affects cross-education of maximal voluntary force Under review. 2020.

437. D'Amico JM, Dongés SC, Taylor JL. High-intensity, low-frequency repetitive transcranial magnetic stimulation enhances excitability of the human corticospinal pathway. Journal of neurophysiology. 2020;123(5):1969-78.

438. Kurz A, Leukel C. Excitability of Upper Layer Circuits Relates to Torque Output in Humans. Frontiers in human neuroscience. 2019;13(359).

439. Kidgell DJ, Pearce AJ. What has transcranial magnetic stimulation taught us about neural adaptations to strength training? A brief review. Journal of strength and conditioning research / National Strength & Conditioning Association. 2011;25(11):3208-17.

440. Hendy AM, Kidgell DJ. Anodal tDCS applied during strength training enhances motor cortical plasticity. Medicine and science in sports and exercise. 2013;45(9):1721-9.

441. Pearce AJ, Hendy A, Bowen WA, Kidgell DJ. Corticospinal adaptations and strength maintenance in the immobilized arm following 3 weeks unilateral strength training. Scandinavian journal of medicine & science in sports. 2013;23(6):740-8.

442. American College of Sports M. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. Medicine and science in sports and exercise. 2009;41(3):687-708.

443. Colomer-Poveda D, Hortobagyi T, Keller M, Romero-Arenas S, Marquez G. Training intensity-dependent increases in corticospinal but not intracortical excitability after acute strength training. Scandinavian journal of medicine & science in sports. 2020;30(4):652-61.

444. Santos W, Vieira C, Bottaro M, Nunes V, Ramirez-Campillo R, Steele J, et al. Resistance training performed to failure or not to failure result in similar total work, but with different fatigue and discomfort levels. The Journal of Strength and Conditioning Research. 2018;Publish Ahead of Print.

445. Zult T, Gokeler A, van Raay J, Brouwer RW, Zijdewind I, Farthing JP, et al. Cross-education does not accelerate the rehabilitation of neuromuscular functions after ACL reconstruction: a randomized controlled clinical trial. European journal of applied physiology. 2018;118(8):1609-23.

446. Manca A, Cabboi MP, Dragone D, Ginatempo F, Ortu E, De Natale ER, et al. Resistance Training for Muscle Weakness in Multiple Sclerosis: Direct Versus Contralateral Approach in Individuals With Ankle Dorsiflexors' Disparity in Strength. Archives of physical medicine and rehabilitation. 2017;98(7):1348-56.e1.

447. Papandreou M, Billis E, Papathanasiou G, Spyropoulos P, Papaioannou N. Cross-exercise on quadriceps deficit after ACL reconstruction. The journal of knee surgery. 2013;26(1):51-8.

448. Ribeiro AS, Dos Santos ED, Nunes JP, Schoenfeld BJ. Acute Effects of Different Training Loads on Affective Responses in Resistance-trained Men. International journal of sports medicine. 2019;40(13):850-5.

449. Levy AR, Polman RCJ, Nicholls AR, Marchant DC. Sport injury rehabilitation adherence: Perspectives of recreational athletes. International Journal of Sport and Exercise Psychology. 2009;7(2):212-29.

450. Magnus CR, Arnold CM, Johnston G, Dal-Bello Haas V, Basran J, Krentz JR, et al. Cross-education for improving strength and mobility after distal radius fractures: a randomized controlled trial. Archives of physical medicine and rehabilitation. 2013;94(7):1247-55.

451. Zult T, Howatson G, Kadar EE, Farthing JP, Hortobagyi T. Role of the mirror-neuron system in cross-education. Sports medicine (Auckland, NZ). 2014;44(2):159-78.

452. Zult T, Goodall S, Thomas K, Hortobagyi T, Howatson G. Mirror illusion reduces motor cortical inhibition in the ipsilateral primary motor cortex during forceful unilateral muscle contractions. Journal of neurophysiology. 2015;113(7):2262-70.

453. Thieme H, Mehrholz J, Pohl M, Behrens J, Dohle C. Mirror therapy for improving motor function after stroke. The Cochrane database of systematic reviews. 2012(3):Cd008449.

454. Goodwill AM, Daly RM, Kidgell DJ. The effects of anodal-tDCS on cross-limb transfer in older adults. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2015;126(11):2189-97.

455. Chan JL, Ross ED. Left-handed mirror writing following right anterior cerebral artery infarction: evidence for nonmirror transformation of motor programs by right supplementary motor area. Neurology. 1988;38(1):59-63.

XVI - ANNEXES

ANNEX 1: Supporting information 1. Trained BB raw values (PRE and POST) and RM-ANOVA of MEP_5% (%M_{max}), MEP_{25}% (%M_{max}), SP (ms), SICI (%TP), ICF (%TP) and M_{max} (mV) before and after every session.

Outcome	PRE	POST	Main effect TIME	Main effect INTENSITY	Interaction TIME x INTENSITY
rmsEMG (%rmsEMG$_{max}$)			F (1, 14) = 0.86; P = 0.37; η_p^2 = 0.06	F (2, 28) = 0.54; P = 0.59; η_p^2 = 0.04	F (2, 28) = 2.18; P = 0.13; η_p^2 = 0.14
CON	2.88 ± 1.58	2.69 ± 1.43			
25	2.79 ± 0.90	2.68 ± 0.87			
75	3.00 ± 0.98	3.07 ± 1.04			
$MEP_{5\%}$ (%M_{max})			F (1, 14) = 2.62; P = 0.13; η_p^2 = 0.16	F (2, 28) = 1.67; P = 0.21; η_p^2 = 0.11	F (2, 28) = 5.06; P = 0.01; η_p^2 = 0.26
CON	7.06 ± 5.98	7.37 ± 8.70			
25	5.95 ± 3.13	6.23 ± 3.83			
75	7.05 ± 4.77	10.34 ± 9.86			
$MEP_{25\%}$ (%M_{max})			F (1, 14) = 0.44; P = 0.52; η_p^2 = 0.03	F (2, 28) = 1.14; P = 0.33; η_p^2 = 0.07	F (2, 28) = 0.90; P = 0.42; η_p^2 = 0.06
CON	49.89 ± 25.53	52.36 ± 24.64			
25	47.48 ± 22.80	46.12 ± 20.85			
75	52.17 ± 18.84	53.00 ± 20.33			
SP (ms)			F (1, 14) = 2.61; P = 0.12; η_p^2 = 0.16	F (2, 28) = 2.58; P = 0.09; η_p^2 = 0.16	F (2, 28) = 0.97; P = 0.39; η_p^2 = 0.06
CON	81 ± 33	84 ± 34			
25	69 ± 20	69 ± 19			
75	77 ± 21	78 ± 21			
SICI (%TP)			F (1, 13) = 1.63; P = 0.22; η_p^2 = 0.11	F (2, 26) = 1.46; P = 0.25; η_p^2 = 0.10	F (2, 26) = 2.66; P = 0.09; η_p^2 = 0.17
CON	79.50 ± 30.16	80.84 ± 27.80			
25	80.27 ± 19.57	79.72 ± 21.91			
75	76.78 ± 31.43	69.11 ± 29.94			
ICF (%TP)			F (1, 14) = 0.16; P = 0.69; η_p^2 = 0.01	F (2, 28) = 0.46; P = 0.64; η_p^2 = 0.03	F (2, 28) = 0.21; P = 0.81; η_p^2 = 0.01
CON	110.04 ± 41.62	105.65 ± 35.27			
25	113.33 ± 26.47	113.70 ± 24.94			
75	113.66 ± 33.55	112.64 ± 20.82			
M_{max} (mV)			F (1, 14) = 1.26; P = 0.28; η_p^2 = 0.08	F (2, 28) = 1.36; P = 0.27; η_p^2 = 0.09	F (2, 28) = 1.60; P = 0.22; η_p^2 = 0.10
CON	6.98 ± 1.63	7.10 ± 1.61			
25	7.31 ± 1.52	7.50 ± 1.52			
75	7.32 ± 1.83	7.27 ± 1.60			

ANNEX 2: Supporting information 2. Untrained BB raw values (PRE and POST) and RM-ANOVA of $MEP_{5\%}$ ($\%M_{max}$), $MEP_{25\%}$ ($\%M_{max}$), SP (ms), SICI (%TP), ICF (%TP) and M_{max} (mV).

Outcome	PRE	POST	Main effect TIME	Main effect INTENSITY	Interaction TIME x INTENSITY
rmsEMG ($\%rmsEMG_{max}$)			F (1, 14) = 0.58; P = 0.46; η_p^2 = 0.04	F (2, 28) = 0.99; P = 0.39; η_p^2 = 0.07	F (2, 28) = 1.35; P = 0.28; η_p^2 = 0.09
CON	4.62 ± 2.11	5.02 ± 2.09			
25	4.81 ± 1.58	4.73 ± 1.79			
75	4.27 ± 2.13	4.18 ± 1.81			
$MEP_{5\%}$ ($\%M_{max}$)			F (1, 14) = 0.61; P = 0.45; η_p^2 = 0.04	F (2, 28) = 0.40; P = 0.67; η_p^2 = 0.03	F (2, 28) = 0.45; P = 0.64; η_p^2 = 0.03
CON	7.31 ± 4.57	7.47 ± 4.44			
25	7.02 ± 4.27	6.38 ± 2.93			
75	7.12 ± 3.85	7.11 ± 3.65			
$MEP_{25\%}$ ($\%M_{max}$)			F (1, 14) = 0.49; P = 0.49; η_p^2 = 0.03	F (1.43, 20.02) = 0.09; P = 0.85; η_p^2 = 0.01	F (2, 28) = 0.99; P = 0.38; η_p^2 = 0.07
CON	53.49 ± 26.30	56.53 ± 27.10			
25	53.89 ± 27.30	53.25 ± 27.85			
75	55.55 ± 31.37	55.18 ± 29.25			
SP (ms)			F (1, 14) = 0.77; P = 0.39; η_p^2 = 0.05	F (2, 28) = 0.23; P = 0.79; η_p^2 = 0.02	F (2, 28) = 0.02; P = 0.97; η_p^2 = 0.01
CON	67 ± 39	66 ± 32			
25	64 ± 27	63 ± 25			
75	64 ± 17	62 ± 20			
SICI (%TP)			F (1, 13) = 1.69; P = 0.27; η_p^2 = 0.11	F (2, 26) = 1.69; P = 0.20; η_p^2 = 0.11	F (2, 26) = 0.18; P = 0.84; η_p^2 = 0.01
CON	75.27 ± 23.28	76.72 ± 29.54			
25	78.87 ± 28.03	80.75 ± 23.33			
75	75.96 ± 27.40	81.27 ± 23.08			
ICF (%TP)			F (1, 14) = 1.07; P = 0.32; η_p^2 = 0.07	F (2, 28) = 0.79; P = 0.46; η_p^2 = 0.05	F (2, 28) = 0.74; P = 0.48; η_p^2 = 0.05
CON	116.42 ± 49.12	108.34 ± 30.00			
25	108.29 ± 28.66	108.53 ± 31.09			
75	116.31 ± 24.24	115.34 ± 23.08			
M_{max} (mV)			F (1, 14) = 3.43 P = 0.08; η_p^2 = 0.20	F (2, 28) = 0.01; P = 0.99; η_p^2 = 0.01	F (2, 28) = 0.06; P = 0.94; η_p^2 = 0.01
CON	7.12 ± 1.43	7.19 ± 1.42			
25	7.09 ± 1.17	7.18 ± 0.99			
75	7.11 ± 1.55	7.24 ± 1.33			

ANNEX 3: Study 1. Reference: Colomer-Poveda D, Romero-Arenas S, Lundbye-Jensen J, Hortobagyi T, Marquez G. Contraction intensity-dependent variations in the responses to brain and corticospinal tract stimulation after a single session of resistance training in men. Journal of applied physiology (Bethesda, Md : 1985). 2019;127(4):1128-39. doi: 10.1152/japplphysiol.01106.2018

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RESEARCH ARTICLE

Contraction intensity-dependent variations in the responses to brain and corticospinal tract stimulation after a single session of resistance training in men

David Colomer-Poveda,[1] Salvador Romero-Arenas,[1] Jesper Lundbye-Jensen,[2] Tibor Hortobágyi,[3] and Gonzalo Márquez[1]

[1]*Department of Physical Education and Sport, Faculty of Sport, Catholic University of Murcia, Murcia, Spain;* [2]*Department of Nutrition, Exercise and Sports, University of Copenhagen, Copenhagen, Denmark; and* [3]*Center for Human Movement Sciences, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*

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Colomer-Poveda D, Romero-Arenas S, Lundbye-Jensen J, Hortobágyi T, Márquez G. Contraction intensity-dependent variations in the responses to brain and corticospinal tract stimulation after a single session of resistance training in men. *J Appl Physiol* 127: 1128–1139, 2019. First published August 22, 2019; doi:10.1152/japplphysiol.01106.2018.—The aim of this study was to determine the effects of acute resistance training (RT) intensity on motor-evoked potentials (MEPs) generated by transcranial magnetic brain stimulation and on cervicomedullary motor-evoked potentials (CMEPs) produced by electrical stimulation of the corticospinal tract. In four experimental sessions, 14 healthy young men performed 12 sets of eight isometric contractions of the elbow flexors at 0 (Control session), 25, 50, and 75% of the maximal voluntary contraction (MVC). Before and after each session, MEPs, CMEPs, and the associated twitch forces were recorded at rest. MEPs increased by 39% ($P < 0.05$ versus 25% in the control condition, Effect size (ES) = 1.04 and 1.76, respectively) after the 50% session and by 70% ($P < 0.05$ vs. all other conditions, ES = 0.91–2.49) after the 75% session. In contrast, CMEPs increased similarly after the 25%, 50%, and 75% sessions with an overall increase of 27% ($P < 0.05$ vs. control condition, ES = 1.34). The amplitude of maximal compound muscle action potentials (M_{max}) was unchanged during the experiment. The MEP- and CMEP-associated twitch forces also increased after RT, but training intensity affected only the increases in MEP twitch forces. The data tentatively suggest that the intensity of muscle contraction used in acute bouts of RT affects cortical excitability.

NEW & NOTEWORTHY Resistance training (RT) can acutely increase the efficacy of the corticospinal-motoneuronal synapse, motoneuron excitability and motor cortical excitability. We show that motor-evoked potential generated by transcranial magnetic stimulation but not cervicomedullary electrical stimulation increased in proportion to the intensity of training used during a single session of RT. The data suggest that the intensity of muscle contraction used in acute bouts of RT affects cortical excitability.

cervicomedullary motor-evoked potentials; cortical excitability; motor-evoked potentials; plasticity; strength training

INTRODUCTION

Resistance training (RT) is widely used to improve maximal voluntary muscle force (MVC) and muscle mass. However, the mechanisms underlying the increases in MVC force following mechanical loading of healthy skeletal muscle remain incompletely understood. Because MVC force increases after a few sessions of RT, before functionally meaningful muscle hypertrophy could occur, the initial adaptations leading to this rapid increase in MVC force are probably of neural origin (1, 2, 15, 23). Indeed, a variety of forms of motor practice can cause rapid adaptations in the central nervous system (CNS) (4, 18, 20, 25, 27, 32, 35, 38). Therefore, the acute changes in the CNS after a single session of RT (18, 19, 27, 35, 38) could act as a trigger for long-term adaptations following repeated training sessions.

This trigger could be an increase in the efficacy of the corticospinal-motoneuronal synapses and increases in motoneuron and/or cortical excitability. In fact, a single session of isometric RT of the elbow flexors increased the size of motor-evoked potentials (MEPs) and cervicomedullary motor-evoked potentials (CMEPs) measured at rest by transcranial magnetic stimulation (TMS) of the motor cortex (M1) and electrical stimulation of the corticospinal tract, respectively (27). CMEPs are affected by peripheral excitability, the efficacy of the corticospinal-motoneuronal synapses and motoneuron excitability, while MEPs are also affected by the excitability of motor cortical neurons. Furthermore, the amplitude of the twitch forces evoked by TMS and electrical corticomedullar stimulation also increased after a session of RT (27). Those involuntary contractions are the sum of the forces produced by different muscles activated by the same nonfocal stimulus. Therefore, these increases in twitch forces toward the trained direction, together with the rise in the amplitude of MEP and CMEPs, suggest that a single session of RT preferentially strengthens the corticospinal-motoneuronal pathway projecting to the trained muscle (27).

The effects of different forms of motor practice on corticospinal excitability can still be present up to an hour after the session (3, 9, 25, 34, 42) and 25 min after RT (27). This lasting increase in corticospinal excitability has been interpreted as a marker of use-dependent corticomotor plasticity probably mediated by mechanisms similar to long-term potentiation (3, 9).

Address for reprint requests and other correspondence: G. Márquez, Facultad de Deporte - Universidad Católica de Murcia, Campus de los Jerónimos s/n Guadalupe, 30107, Murcia, Spain (e-mail: gmarquez@ucam.edu).

Most acute RT studies have used high-intensity muscle contractions as an exercise stimulus. However, low- compared with high-intensity (36) RT can also improve MVC force, albeit to a lesser extent. Because the hypertrophy response to RT seems to be independent of intensity, the differences in the increases in MVC force brought about by low- and high-intensity RT may be related to differences in neural adaptations.

Contraction intensity affects the magnitude of corticospinal tract activation (8, 21, 31, 41). At the spinal level, stronger contraction intensities implicate higher motoneuronal excitability through presynaptic and postsynaptic mechanisms, increased motor unit recruitment and higher firing frequencies (24). This leads to an increase in CMEP amplitude with contraction intensity until a decrease during very strong contractions, which is proposed to relate to motoneuron afterhyperpolarization trajectory (21). Similar to CMEP amplitude, MEP amplitudes also increase with contraction intensity (21, 31, 41), even though such responses to TMS tend to saturate and may even decrease before reaching 100% of MVC force (21, 39). Spinal mechanisms (increased motoneuron pool excitability) could account for the increase in MEP amplitude; however, the intensity of the contraction also influences the cortical output neurons and interneurons involved in generating the descending commands, as shown by neuroimaging studies and direct epidural recordings (8, 10). Additionally, the GABAergic mediated intracortical inhibition progressively decreases with the intensity of the contraction (30). Thus, it is conceivable that high- compared with low-intensity RT has a greater potential to induce neural adaptations. Whether the lasting effects on corticospinal and spinal motoneurons occur in a dose-dependent manner after a single RT session using low-skill, invariant isometric muscle contractions, are unknown.

Therefore, the purpose of the present study was to determine the effects of acute RT intensity on the electromyographic (EMG) responses [MEPs, CMEPs, and maximal compound muscle action potential (M_{max})] and twitch forces evoked by brain and corticospinal tract stimulation. We administered all tests at rest to control for motoneuron excitability and because measurements at rest are sensitive to RT-induced changes in the CNS (27). We compared these outcomes for up to 30 min following RT at 25%, 50%, and 75% MVC, and a control resting condition (CON). We hypothesized that MEPs, CMEPs, and the associated twitch forces would increase in an intensity-dependent manner after a bout of RT.

MATERIALS AND METHODS

Participants

Healthy, right-handed, and recreationally active men (2–3 h/wk of recreational sports activities or aerobic training, age, 23.5 ± 3.93 yr; $n = 16$) without contraindications to TMS and currently not taking any medications, participated in the study. Data from two participants were excluded from the analyses because it was not possible to evoke CMEPs with a constant latency >7.5 ms. Participants came to the laboratory 1 wk before the start of the experiments to become familiar with the MVC task, peripheral nerve stimulation, TMS, and corticospinal tract stimulation. Participants were asked to refrain from consuming caffeinated or alcoholic drinks and exercising 24 h before each testing session. The Institutional Review Board approved the protocol and the informed consent form, which all participants signed before the start of the experiments. The study was conducted in accordance with the latest version of the Declaration of Helsinki.

Set-Up

Participants were seated in a chair in front of a table with the right shoulder flexed at ~90° and the elbow flexed with forearms placed vertically (Fig. 1*A*). Right forearm was supinated and strapped at the wrist to a force transducer (NL63, 200 kg; Digitimer, Welwyn Garden City, UK) that measured voluntary and evoked twitch forces. The left arm rested on the table during the experiments. Visual feedback of voluntary elbow flexion force was displayed on a computer screen in front of the participant.

Surface EMG activity was recorded from the right and left biceps brachii (BB) using Ag-AgCl surface electrodes (5–8 cm interelectrode distance) attached to the skin with a belly-tendon montage. EMG signals were amplified (×200 to ×300), band-pass-filtered (10–1,000 Hz), and sampled at 2 kHz with a Digitimer d440 isolated amplifier (Digitimer). Force recordings were band-pass-filtered (5–2,500 Hz), amplified (×2,500), and sampled at 2 kHz using a Neurolog System (Digitimer). Both EMG and force signals were simultaneously collected using an analog-to-digital board CED Micro1401-3 (Cambridge Electronic Design, Cambridge, UK) for further analysis.

Brachial Plexus Stimulation

M_{max} of the right BB was obtained via a single electrical stimulus delivered to the right brachial plexus (200-μs duration, DS7AH constant current stimulator; Digitimer). The cathode (pregelled Ag-AgCl electrodes) was positioned in the supraclavicular fossa, and the anode was placed on the acromion. Stimulation intensity (range 40–168 mA) was set to 120% of what was needed to produce a maximal size M-wave in the right BB. A supramaximal stimulus was used to reduce the probability that some axons would remain inactivated because of axonal hyperpolarization due to fatigue (33). Twitch forces associated with each M_{max} were also recorded.

Transcranial Magnetic Stimulation

We generated MEPs in the right BB by placing a figure-of-eight coil (70-mm diameter; stimulator: DuoMag, Rogue Resolutions, Cardiff, UK) over an optimal spot of the left M1. The optimal site was obtained by exploring the estimated center of the BB motor cortical representation (4–7 cm lateral to the vertex). The hot spot, i.e., where a known suprathreshold intensity produced the largest responses, was marked on the scalp with a permanent marker. The coil was oriented with the handle pointing backward and laterally at around 45° to the midline. The stimulation intensity (58%–100%) that induced an MEP of ~2–5% of the M_{max} amplitude, was determined at rest, and used to test the effects of acute RT on corticospinal excitability. Such a measure is sensitive to RT-induced neural adaptations (27). Peak twitch forces associated with MEPs were also recorded.

Electrical Stimulation of the Corticospinal Tract at the Cervicomedullary Junction

Motor responses of the right BB were also obtained by electrically stimulating the corticospinal axons at the cervicomedullary junction. Pregelled Ag-AgCl electrodes were affixed over the left (cathode) and right (anode) mastoid process. Stimulation intensity (90–226 mA, 200-μs duration) was set to produce a CMEP of 10–20% of M_{max} with the right BB at rest. Such a measure is sensitive to adaptations in motoneuron excitability or the efficacy of the corticospinal-motoneuronal synapses induced by RT (27). Peak-to-peak twitch forces associated with each CMEP were also recorded.

Experimental Procedures

Main experiment. Each subject completed four experimental sessions separated by 5–7 days in a random order: isometric RT at 0%,

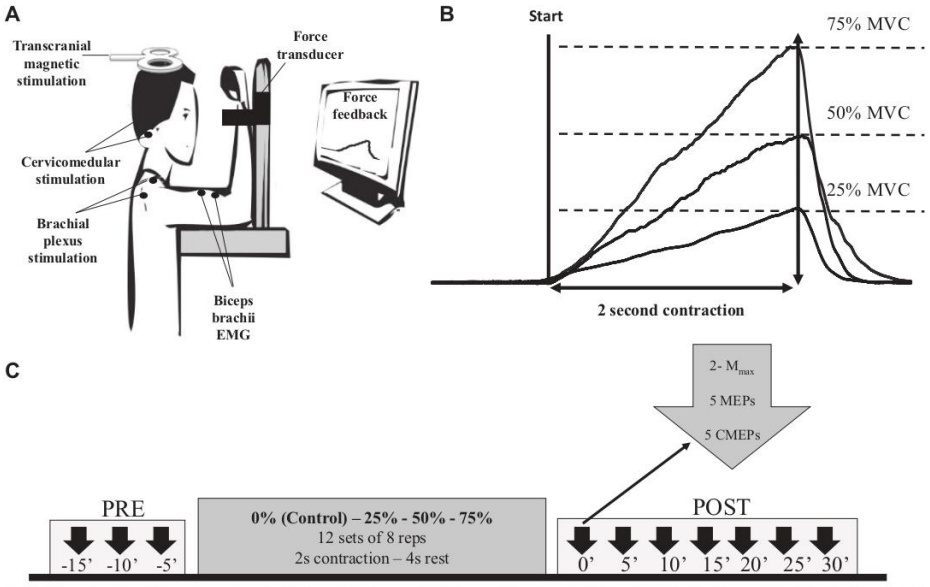


Fig. 1. Schematic view of the set-up and protocol. *A*: participants completed the experiment comfortably seated with the elbow and the shoulder flexed to 90° in front of a screen showing the force feedback. *B*: raw traces of a contraction from each training session from a representative subject. In each training session, the time in which participants have to steadily contract was identified with two vertical bars, and the intensity required was marked with a horizontal dashed line. *C*: motor-evoked potentials and associated twitches were obtained before (PRE) and after (POST) each training (at 25, 50, or 75% of maximum voluntary contraction, MVC) or control session (20 min of rest).

25%, 50%, and 75% of MVC. The 0% or control session consisted of 20 min of sitting at the table used for RT.

Training consisted of 12 sets of eight, slowly ramped isometric contractions of the elbow flexors with 4 s of rest between contractions and 1 min of rest between sets. Marked by a 2-s-long window, participants ramped up force to 25%, 50%, or 75% of MVC represented by a horizontal line displayed on a monitor and relaxed as soon as they reached the target force at the end of the 2-s period (see Fig. 1*B*). The rate of force development was, thus, different between sessions.

During each session, participants performed three measurement blocks involving noninvasive stimulation 15, 10, and 5 min before RT. Immediately after RT, participants performed one measurement block (POST-0') that was repeated 5, 10, 15, 20, 25, and 30 min after POST-0'. The number of stimuli in each block was identical to a protocol reported previously (27): with two initial M_{max} measurements, five CMEPs, and five MEPs elicited in a random order with both arms at rest. EMG of both BBs was monitored, and participants were repeatedly reminded to relax both arms.

After PRE measurements and before each intervention, all participants performed 2 or 3, 3–5-s-long isometric elbow flexion MVCs with 90 s of rest between trials. The highest value of all the attempts was used to determine the training intensity for that session.

Complementary experiment. While contraction intensity differed between sessions (25%, 50%, and 75% of MVC), each session comprised 12 × 8, i.e., 96 contractions. Thus, the total amount of physiological work performed differed between sessions. In a complementary experiment, we, therefore, examined the effects of the exercise volume on measures of neural adaptations. Participants (n = 8) performed an additional session at 25% of MVC but with twice the volume used in the main experiment (i.e., 2 × 12 = 24 sets). Thus, the total amount of physiological work corresponded to work produced in the 50% session.

Data Analysis

We measured the peak-to-peak amplitudes of M_{max}, MEPs, and CMEPs, and MEPs and CMEPs were normalized to M_{max} within each measurement block and averaged. PRE measurements were represented as the average of all responses obtained in the three PRE blocks (i.e., PRE −15, −10, and −5 min). We also measured the peak-to-peak twitch force amplitudes by calculating peak-to-peak values over a 200-ms time window after the stimulation.

To assess neuromuscular performance, we averaged the root mean square (RMS) amplitude of the surface EMG activity (normalized for M_{max} recorded in each session) and the impulse (force × time) within each of four 500-ms-long window (from 0 to 2 s; i.e.: 0–0.5; 0.5–1; 1–1.5; 1.5–2 s) during every 2-s contraction.

Statistics

Normality was confirmed using the Kolmogorov-Smirnov test. Intrasession and intersession reliability for M_{max}, MEPs, CMEPs, their associated twitches, and stimulation intensities, was determined using intraclass correlation coefficients (ICCs) with 95% confidence intervals (95% CIs) from the mixed-effect model. The ICC was interpreted with values below 0.5, 0.5 to 0.75, 0.75 to 0.90, and >0.90

indicating, respectively, low, moderate, good, and excellent reliability (16). To analyze neuromuscular performance during each training session, a two-way RM-ANOVA was performed with Set (1–12) and Interval (1st, 2nd, 3rd, and 4th) as factors for the EMG-RMS and the impulse (force area under the curve). A one-way repeated-measures (RM) analysis of variance (ANOVA) with Intensity as factor was performed for PRE-test measurements for M_{max}, MEPs, CMEPs, and their associated twitches to detect any between-group differences at baseline. Because there were no between-group differences in the baseline values, the subsequent analyses were performed with each session data normalized to its PRE values (i.e., on the Pre- to Post-trial change scores). A two-way RM-ANOVA was performed with Time (Pre, POST-0', POST-5', POST-10', POST-15', POST-20', POST-25', and POST-30') and Intensity (CON, 25%, 50%, and 75%) as factors for the M_{max}, MEPs, CMEPs, and their associated twitch forces (all normalized to PRE values). For the complementary experiment, a two-way RM-ANOVA was performed with Time (PRE, POST-0', POST-5', POST-10', POST-15', POST-20', POST-25', POST-30') and Volume as factor (25% and 25% × 2) for M_{max}, MEPs, CMEPs, and their associated twitch forces. The main effect of Intensity or Volume was also analyzed independently of the other main effects or interactions to detect the overall effect of every session on each variable during the 30-min postintervention. If sphericity was violated (Mauchly's test), degrees of freedom were corrected by Greenhouse-Geisser estimates of sphericity. Bonferroni correction was applied for post hoc analyses to account for multiple comparisons. Effect sizes are presented as partial η-square values (η_p^2; small: 0.02; medium: 0.13; large: 0.26) (5). Unless indicated otherwise, data are reported as means ± SD. SPSS 20.0 software (SPSS, Chicago, IL) was used for statistical analysis. Statistical significance was set at $P \leq 0.05$.

RESULTS

Main Experiment

Reliability. Intrasession reliability of M_{max}, MEPs, and CMEPs and the associated twitches was good to excellent (ICC = 0.88 to 0.99, Table 1). Intersession reliability for M_{max}, MEPs, and CMEPs and the associated twitches and stimulation intensities was moderate to excellent (ICC = 0.67 to 0.98 Table 1).

Neuromuscular performance. The two-way RM-ANOVA revealed that force impulse increased linearly from the beginning to the end of the contraction for all the intensities (Fig. 2*A*). Furthermore, the impulse remained unaltered across the sets. EMG activity normalized with the M_{max} of each session, increased linearly from the beginning to the end of the contractions for each set and intensity and remained stable across the sets (Fig. 2*B*).

MEP Amplitudes and Associated Twitch Forces

Figure 3 shows a representative individual example of MEPs and CMEPs obtained at rest after control, and acute RT at 25%, 50%, and 75% of MVC. MEP amplitudes increased more after RT at 75% compared with all the other sessions. Figure 4 shows that there were Time [F (7,91) = 10.14, $P < 0.001$; $\eta_p^2 = 0.44$], Intensity [F (3,39) = 20.17, $P < 0.001$; $\eta_p^2 = 0.61$] and Time × Intensity interaction effects [F (21,273) = 3.55, $P < 0.001$; $\eta_p^2 = 0.21$]. Overall, MEPs consistently increased over the 30 min after RT compared with baseline only after 75% session. The 50% session increased MEPs from 0' to 15', but the 25% and control sessions did not affect MEP size. The 75% session compared with other sessions produced the largest increases in MEP size during the last 15' (Fig. 4). Also, the Intensity main effect revealed greater sustained increases in MEPs after RT at 75% (+69.6%) compared with control (−5.3%, $P = 0.001$), 25 (+10.6%, $P = 0.001$), and 50% (+39.2%, $P = 0.026$) of MVC and also after RT at 50% versus control ($P = 0.008$) and 25% ($P = 0.024$) MVC (Fig. 4*B*).

Table 1. *Mean PRE values for M_{max}, MEP/M_{max}, and CMEP/M_{max} and its associated twitches and intrasession and intersession reliability*

	Session	PRE Value	Intrasession ICC (95% CI)	Intersession ICC (95% CI)
M_{max}, mV	CON	5.99 (1.60)	0.99 (0.97, 0.99)	0.97 (0.93, 0.99)
	25	6.14 (1.59)	0.99 (0.97, 0.99)	
	50	5.84 (1.52)	0.99 (0.99, 0.99)	
	75	5.90 (1.78)	0.99 (0.99, 0.99)	
MEP/M_{max}, % M_{max})	CON	5.59 (2.54)	0.90 (0.76, 0.97)	0.93 (0.87, 0.97)
	25	4.26 (1.87)	0.94 (0.84, 0.98)	
	50	5.69 (4.35)	0.93 (0.84, 0.98)	
	75	4.57 (2.31)	0.93 (0.84, 0.98)	
CMEP/M_{max}, % M_{max}	CON	11.29 (5.12)	0.82 (0.57, 0.94)	0.67 (0.33, 0.88)
	25	10.93 (7.35)	0.96 (0.91, 0.99)	
	50	10.66 (5.55)	0.95 (0.88, 0.98)	
	75	9.87 (5.07)	0.88 (0.72, 0.96)	
$M_{max\text{-}twitch}$, N	CON	27.29 (7.79)	0.96 (0.91, 0.99)	0.94 (0.89, 0.98)
	25	29.53 (10.79)	0.96 (0.91, 0.99)	
	50	33.86 (8.81)	0.96 (0.91, 0.99)	
	75	31.56 (12.42)	0.99 (0.97, 0.99)	
$MEP_{-twitch}$, N	CON	2.36 (1.08)	0.96 (0.90, 0.99)	0.95 (0.91, 0.98)
	25	2.34 (1.38)	0.94 (0.85, 0.98)	
	50	2.55 (1.52)	0.98 (0.95, 0.99)	
	75	1.87 (0.98)	0.95 (0.88, 0.98)	
$CMEP_{-twitch}$, N	CON	6.43 (2.92)	0.97 (0.94, 0.99)	0.91 (0.82, 0.97)
	25	6.21 (2.20)	0,98 (0,94, 0,99)	
	50	6.07 (2.89)	0.93 (0.83, 0.98)	
	75	5.59 (2.15)	0.96 (0.89, 0.98)	

PRE values are expressed as means (SD). CI, confident interval; CMEP, cervicomedullary motor evoked potential; ICC, intraclass correlation coefficient; M_{max}, maximal compound muscle action potential; MEP, motor-evoked potential.

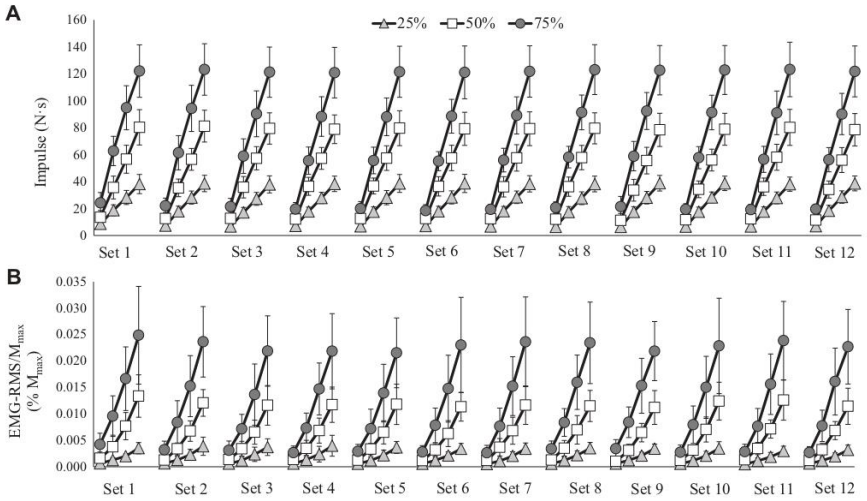


Fig. 2. Force and muscle activity (EMG) during resistance training (n = 14 males). Impulse (*A*) and EMG-root mean square (RMS)/M_{max} (*B*) from the eight repetitions of each set (1st–12th) during each training intervention (25%, 50%, and 75% MVC) in the main experiment (means ± SD). Results from each set are divided into four time intervals of 500 ms.

MEP twitch forces increased more after RT at 75% than after the other sessions. There were Time [F (2.84,36.98) = 23.83, P < 0.001; η_p^2 = 0.65], Intensity [F (1.49,19.42) = 28.66, P < 0.001; η_p^2 = 0.69], and Time × Intensity interaction effects [F (21,273) = 5.44, P < 0.001; η_p^2 = 0.29]. As with MEPs, MEP twitch forces consistently increased over the 30 min of measurements after RT with 75% MVC compared with baseline. The 50% session also increased MEP twitch forces compared with baseline but only immediately after training (0'). No changes occurred after the 25% and control sessions relative to baseline. Increases after RT with 75% were larger compared with the other sessions during the last 15 min (Fig. 5). Furthermore, the main effect of Intensity showed that the increases in MEP-associated twitch forces were the greatest after the 75% session (+83.1%; Control session: −9.8%; 25% session: +18.2%; 50% session: +38.5%, all P < 0.001, see Fig. 5*B*). The overall increases in MEP-associated twitch forces were also greater after RT at 25% and 50% compared with control session (P = 0.016 and P = 0.009, respectively; see Fig. 5*B*).

CMEP Amplitudes and Associated Twitch Forces

CMEP amplitudes after acute RT were larger compared with the control session, independent of the intensity. There were Time [F (2.66,34.53) = 4.30, P = 0.014; η_p^2 = 0.25] and Intensity [F (3,39) = 7.15, P = 0.001; η_p^2 = 0.34] main effects but no Time × Intensity interaction [F (21,252) = 1.24, P = 0.217; η_p^2 = 0.09]. Overall, there was an increase in CMEP amplitude after RT at any intensity (mean of +26.9%) compared with the control session (−14.9%, all P < 0.05 for all comparisons) but without differences between the other sessions (Fig. 4*D*). The increase after RT sessions was not different to baseline values at any point (Fig. 4*C*).

CMEP-associated twitch forces after acute RT were larger compared with the control session, independently of the intensity. There were Time [F (3.33,43.36) = 9.55, P < 0.001; η_p^2 = 0.42], Intensity [F (3, 39) = 7.75, P < 0.001; η_p^2 = 0.37] and a Time × Intensity interaction [F (21,273) = 3.53, P < 0.001; η_p^2 = 0.21] effects. CMEP-associated twitch forces increased compared with baseline values only from 0' to 10' after RT at 50% and 75% of MVC (Fig. 5*C*). The increase after 25%, 50%, and 75% sessions was only different compared with the control session during the first 20' (Fig. 5*C*). Also, the main effect of Intensity showed that CMEP-associated twitch forces after 25%, 50%, and 75% sessions (mean of +31.3%) was larger than the increase after the control session (−5%, all P < 0.05 for all comparisons) but without statistical differences between training at 25%, 50%, and 75% of MVC (Fig. 5*D*).

Maximal M-wave amplitudes and associated twitch forces

M_{max} amplitude did not change after any intervention (Fig. 4, *E* and *F*). M_{max}-associated twitch forces increased immediately after acute RT and then returned to baseline values. There were Time [F (2.25,29.29) = 58.35, P < 0.001; η_p^2 = 0.82] Intensity [F (3,39) = 5.31, P = 0.004; η_p^2 = 0.29] and Time × Intensity interaction [F (21,273) = 15.67, P < 0.001; η_p^2 = 0.55] effects. M_{max} twitch forces increased compared with baseline immediately after 25%, 50%, and 75% sessions (0' after RT, P = 0.003, P < 0.001, and P = 0.001, respectively). The increase in the M_{max}-associated twitch forces immediately after training (from 0' after RT) was larger after the 50% and

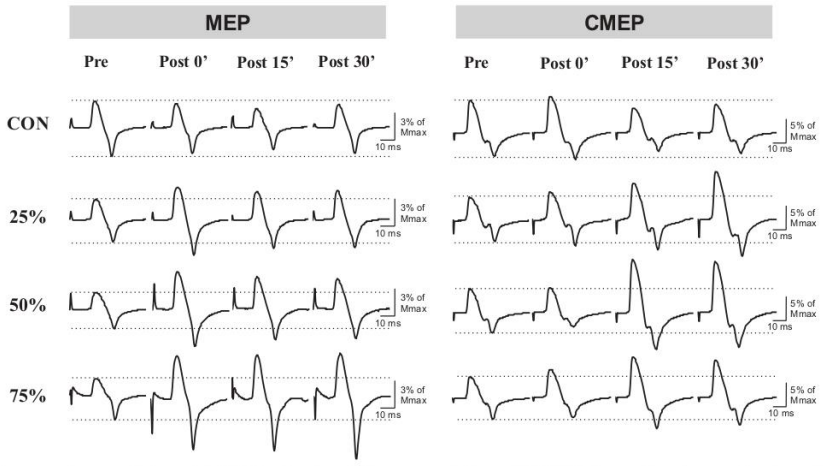


Fig. 3. Raw traces of motor evoked potentials (MEPs) and cervicomedullary motor evoked potentials (CMEPs) in one subject after control session and isometric resistance training at 25%, 50%, and 75% of maximum voluntary contraction (MVC). PRE motor-evoked potentials represent the average of all of the evoked potentials obtained at 15, 10, and 5 min before training. POST-0', POST-15', and POST-30' represents the average of all evoked potentials obtained at each time point. Dashed line indicates the amplitude of PRE measurements.

the 75% session compared with the control and 25% sessions. The Intensity main effect showed that M_{max} twitch forces did not differ between sessions ($P > 0.05$; see Fig. 5*F*).

Complementary Experiment

MEP amplitudes and associated twitch forces. Doubling the volume of RT at 25% of MVC produced larger MEP amplitudes. There were Time [F (7,49) = 6.97, $P < 0.001$; $\eta_p^2 = 0.50$] and Volume effects [F (1,7) = 11.53, $P = 0.012$; $\eta_p^2 = 0.62$] but not a Time × Volume interaction [F (2.90,20.29) = 2.10, $P = 0.61$; $\eta_p^2 = 0.23$]. The increase in MEP amplitude was larger after performing 24 sets instead of 12 sets at 25% of MVC ($P = 0.012$; see Fig. 6*A*). However, pairwise comparisons for the main effect of time showed larger MEP amplitudes compared with baseline only at 0' and 10' after both training sessions ($P = 0.047$ and $P = 0.022$, respectively).

Performing 24 sets instead of 12 at 25% of MVC produced also larger increases in MEP-associated twitch forces ($P = 0.037$; see Fig. 6*B*). There were Time [F (2.35,16.43) = 14.02, $P < 0.001$; $\eta_p^2 = 0.67$], Volume [F (1,7) = 6.64, $P = 0.037$; $\eta_p^2 = 0.49$] and Time × Volume interaction [F (7,49) = 3.29, $P = 0.006$; $\eta_p^2 = 0.32$] effects. However, pairwise comparisons showed that MEP-associated twitch forces were not significantly different compared with baseline after any training session. The increase in MEP-associated twitch forces was significantly larger after performing 24 sets compared with 12 sets at 25% only at 0' after RT ($P = 0.035$).

CMEP amplitudes and associated twitch forces. CMEP amplitude and CMEP-associated twitch forces did not change after any intervention (Fig. 6, *C* and *D*).

M_{max} amplitudes and associated twitch forces. For M_{max} obtained at rest, there was a Volume [F (1,7) = 5.96, $P = 0.045$; $\eta_p^2 = 0.46$] main effect but not a Time [F (1.92,13.42) = 1.56, $P = 0.171$; $\eta_p^2 = 0.18$] or Time × Volume interaction [F (3.41,23.85) = 2.51, $P = 0.77$; $\eta_p^2 = 0.26$] effect. Pairwise comparisons showed a statistically larger increase in M_{max} after performing 24 sets compared with 12 sets at 25% ($P = 0.045$; see Fig. 6*E*).

For M_{max}-associated twitch forces, there was a main effect of Time [F (3.09,21.62) = 12.93, $P < 0.001$; $\eta_p^2 = 0.65$] but not Volume [F (1,7) = 1.52, $P = 0.257$; $\eta_p^2 = 0.18$] or Time × Volume interaction [F (7,49) = 0.84, $P = 0.557$; $\eta_p^2 = 0.11$] effect. Pairwise comparisons showed a statistically larger increase in M_{max} twitch forces compared with baseline only at 0' after RT, independent of training volume ($P = 0.031$).

DISCUSSION

Main experiment. The data show for the first time that the intensity of acute isometric RT of the elbow flexors affects cortical excitability measured at rest in healthy men. In agreement with the hypothesis, MEP amplitude and the associated twitch forces increased with RT intensity but, contrary to the hypothesis, the changes in CMEP amplitude and twitch forces were independent of RT intensity. Also, the duration of the effect on TMS responses increased with RT intensity. The data suggest that the intensity of muscle contraction used in acute bouts of RT affects cortical excitability.

Our results expand previous data by showing dose-response effects of RT intensity on corticospinal excitability measured at rest. Acute bouts of RT can increase the responses to stimulation of the corticospinal tract at cortical (18, 19, 27, 35, 38) and

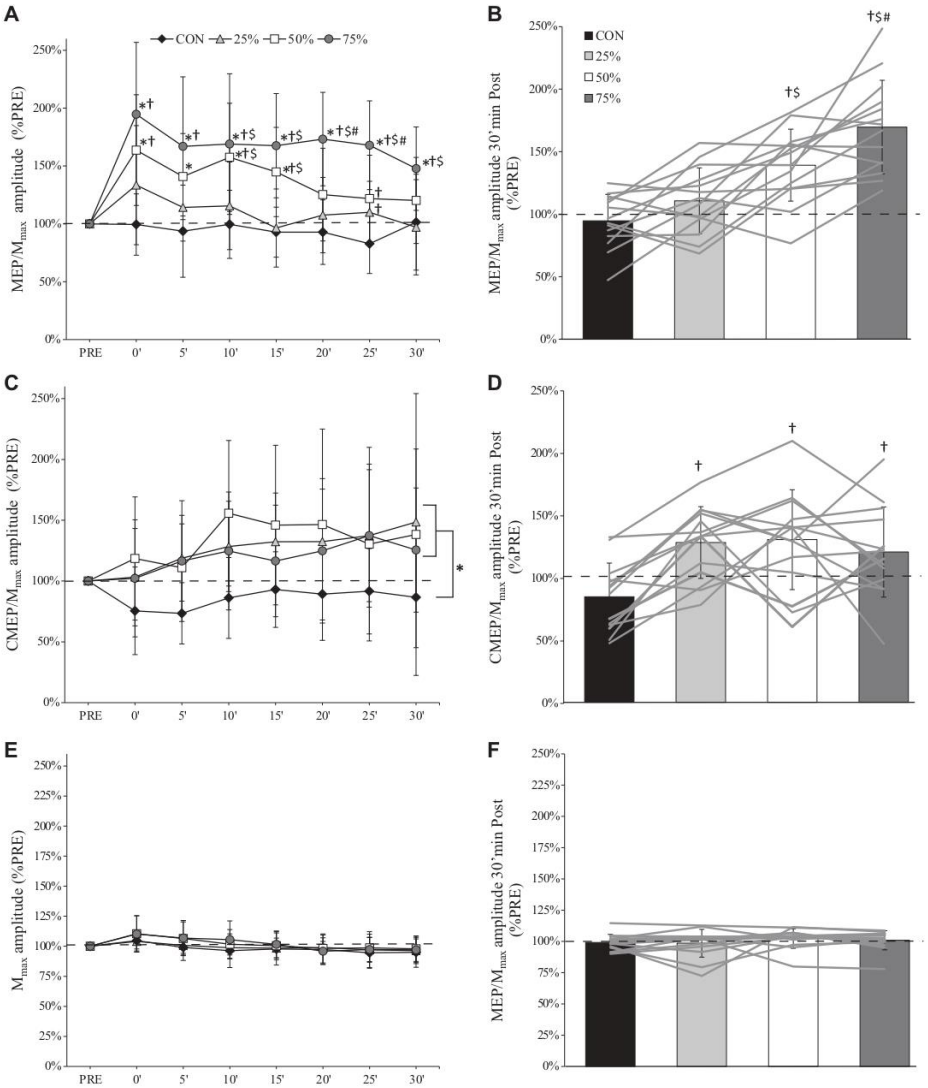
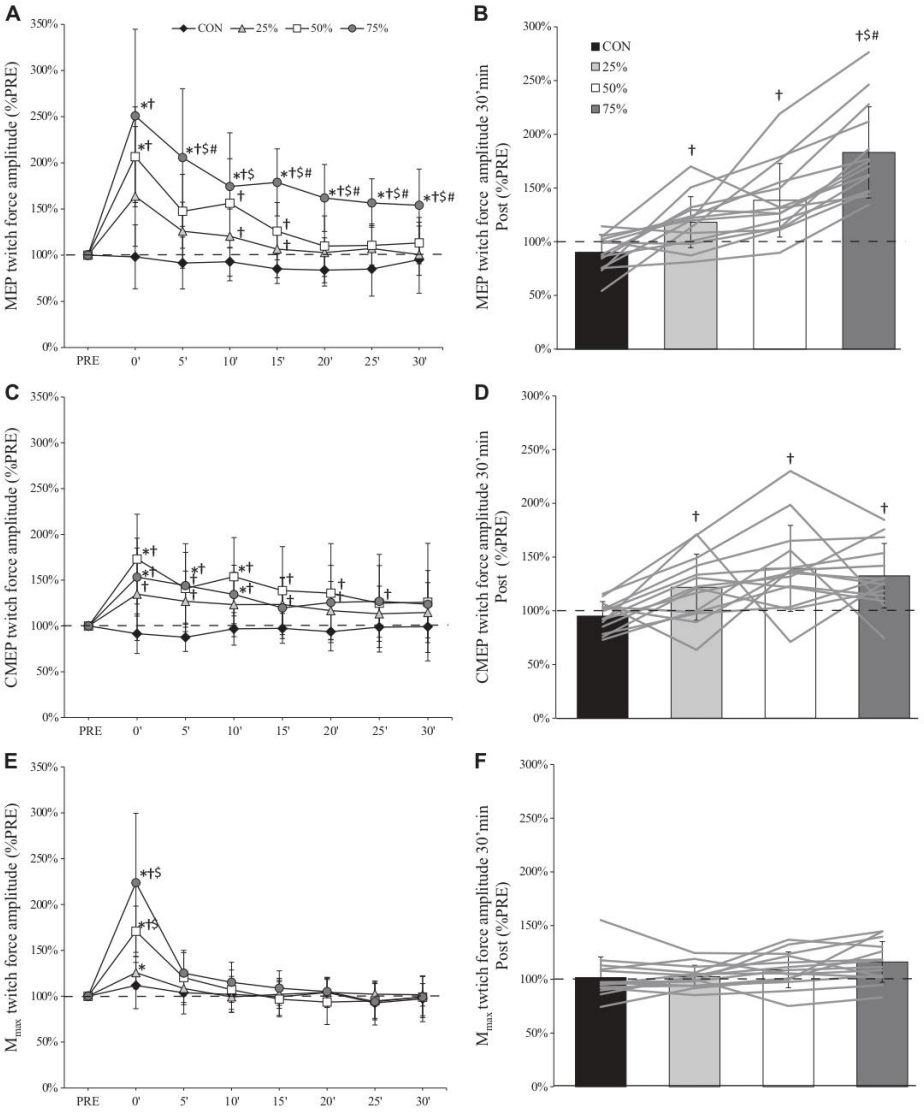


Fig. 4. Time course of motor evoked potentials (MEPs), cervicomedullary motor evoked potentials (CMEPs), and M_{max} after resistance training (n = 14 males). *Left*: time course (means ± SD) of the MEP/M_{max} (*A*), CMEP/M_{max} (*C*), and M_{max} (*E*) of the right biceps brachii during the different RT sessions performed at 25%, 50%, and 75% of the maximum voluntary contraction (MVC) and during the control (CON) condition (two-way repeated measures (RM)-ANOVA with Time and Intensity as factors). Each evoked potential was normalized to PRE values. *Right*: the Intensity main effect for the MEP/M_{max} (*B*), CMEP/ M_{max} (*D*), and M_{max} (*F*) of right biceps brachii. *Statistically significant difference ($P < 0.05$) to PRE values. †Statistically significant ($P < 0.05$) with respect to CON ($P < 0.05$). $Statistically significant difference ($P < 0.05$) with respect to 25%. #Statistically significant difference ($P < 0.05$) with respect to 50%.



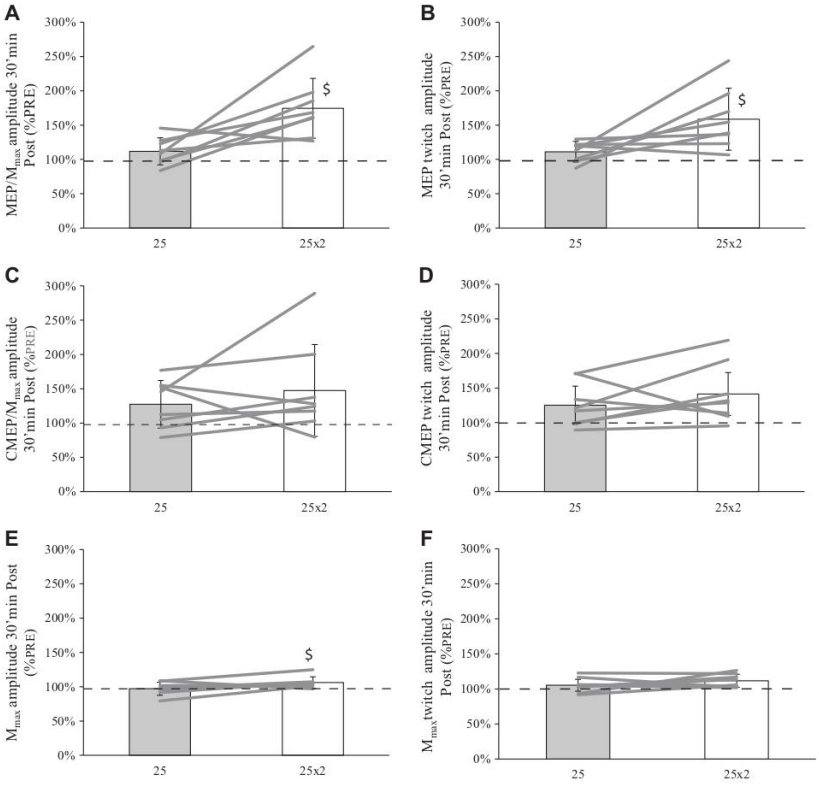


Fig. 6. Volume main effect for motor-evoked potentials (MEPs), cervicomedullary motor-evoked potentials (CMEPs), and M_{max} and associated twitches after low-intensity and double volume low-intensity resistance training [n = 8 males, two-way repeated measures (RM)-ANOVA]. *Left*: overall net change [i.e., average of all measures obtained after each training session normalized to PRE values (means ± SD)] for the MEP/M_{max} (*A*), CMEP/M_{max} (*C*), and M_{max} (*E*) of right biceps brachii. *Right*: overall net change (i.e., average of all measures obtained after each training session normalized to PRE values) for the associated twitches of the MEP/M_{max} (*B*), CMEP/M_{max} (*D*), and M_{max} (*F*) of the right biceps brachii. $Statistically significant difference ($P < 0.05$) with respect to 25%.

spinal levels (27), suggesting an increase in cortical or motoneuron excitability or an increase in the efficacy of the corticospinal-motoneuronal synapse. Our results show that CMEPs and associated twitch forces increased after RT independent of training intensity in comparison to the control session. However, CMEPs were not different to baseline after RT (Fig. 4*C*), suggesting that spinal adaptations measured at rest after acute RT do not always occur (28).

Regarding responses to TMS, our data show that MEPs measured at rest increased by 95%, 64%, and 35% just a minute after the last contraction of an acute bout of isometric RT at 75%, 50%, and 25% of MVC and that the increase after

Fig. 5. Time course of motor evoked potentials (MEPs), cervicomedullary motor-evoked potentials (CMEPs), and M_{max} twitch forces after resistance training (n = 14 males). *Left*: time course (means ± SD) of the associated twitches of MEP (*A*), CMEP (*C*), and M_{max} (*E*) of the right biceps brachii during the different RT sessions performed at 25%, 50%, and 75% of the maximum voluntary contraction (MVC) and during the CON condition (two-way RM-ANOVA with Time and Intensity as factors). Each twitch was normalized to the PRE values. *Right*: main effect of Intensity for the associated twitches of the MEP/M_{max} (*B*), CMEP/M_{max} (*D*), and M_{max} (*F*) of the right biceps brachii. *Statistically significant difference ($P < 0.05$) to PRE values. †Statistically significant ($P < 0.05$) with respect to CON ($P < 0.05$). $Statistically significant difference ($P < 0.05$) with respect to 25%. #Statistically significant difference ($P < 0.05$) with respect to 50%.

RT at 75% was larger compared with the increases after RT at lower intensities. Considering the 75% condition, the 95% increase was smaller than the 242% increase reported previously (27), a difference that could be related to the position of the shoulder being flexed to 90° and forearm supinated versus shoulder abducted and forearm pronated (27). Such differences in joint positions could affect the responses to TMS and cervicomedullary stimulation (7, 29). Also, in our study, the rate of force development (RFD) systematically increased with contraction intensity and could confound the observed dose effects. However, RFD does not seem to be a determinant of corticospinal responses to acute RT (27, 38).

When normalized to M_{max}, the responses to M1 stimulation by TMS involve cortical and spinal mechanisms (40). However, motoneuron excitability and the efficacy of the corticospinal-motoneuronal synapse are the mechanisms involved in CMEPs normalized to M_{max}, which did not vary with RT intensity. Furthermore, contrary to MEPs, CMEPs did not increase immediately after RT. Thus, it seems that the intensity-dependent TMS responses to RT reflect cortical involvement. Indeed, Dai et al. (8) showed that higher forces led to correlated increases in activation of motor cortical neurons and interneurons to generate the desired motor output. Furthermore, there is additional evidence for a lack of adaptation at the spinal level after short duration high-intensity RT as measured by cervicomedullary stimulation (28) and H-reflex (12). Thus, the emerging picture is that initial neural adaptations to RT are localized at a supraspinal level (12). The increases in MEP size after RT are probably a reflection of changes in excitatory-inhibitory balance toward greater efficacy of the excitatory input to the trained muscles. One way this can happen is that cortical excitability increases, while the efficacy of GABAergic inhibitory interneurons decreases, or both (17, 19, 22).

The MEP- and CMEP-associated twitch forces also increased after RT, but training intensity affected only the increases in MEP twitch forces. Twitch forces evoked by nonfocal stimulation like TMS or corticospinal tract electrical stimulation reflect the sum of the forces of different muscles around the joint, including the antagonist elbow extensors (27). Therefore, although not intensity-dependent, the increase in the twitch force elicited by cervicomedullary electrical stimulation during the first 10 min reflects some increase in motoneuron excitability or the efficacy of the corticospinal-motoneuronal synapse (27), occurring preferentially in the motoneurons projecting to the elbow flexors. Also, the intensity-dependent increase in the twitch forces evoked by TMS reflects that the intensity of training influenced the increase in the output of the cortical neurons projecting mainly to the elbow flexors. Some potentiation at the peripheral level also occurred because the M_{max}-associated twitch forces increased immediately after the protocol. This potentiation could have influenced the increase in MEP- and CMEP-associated twitch forces after RT during the first 10 min but probably did not influence the rest of measurements (27).

Our results show that not only did RT intensity affect the magnitude of increases in cortical excitability, it also affected its duration. This longer-lasting effect is probably related to the larger increase produced by the higher intensities immediately after RT ended. However, as was the case for magnitude, the duration of the effect of RT in CMEPs was independent of exercise intensity. The dose-dependent lasting rise in cortical excitability could be related to use-dependent corticomotor plasticity mediated by (LTP)-like mechanisms (3, 9), which can be present up to an hour after motor practice is stopped (3, 9, 25, 34, 42). However, previous studies questioned the role of plastic changes in the corticospinal pathway measured by TMS in the neural adaptations to simple RT tasks (14). Therefore, it is possible that the characteristics of the task, generating progressively higher force in response to the visual cue, and not RT per-se, could underlie the acute corticospinal responses that we observed. Indeed, corticospinal excitability increases and cortical inhibition decreases after skill training and metronome-paced RT but not self-paced RT (14, 19). This suggests that synchronization to a visual or audible cue could be more important to modulate the neural mechanisms than contraction intensity per se. However, our results show that in a task in which participants increase force by tracking a visual template, cortical responses to TMS scale with contraction intensity, leading to an effort-dependent sensitization of cortico-cortical cells in M1 that strengthens the intracortical neuronal ensembles generating outputs toward the trained muscles (3).

The increase in the net excitatory output from M1 measured by single-pulse stimuli could be related to a compensatory mechanism to counteract peripheral fatigue (18). However, although we cannot discard the presence of some peripheral fatigue, it was probably low, since there were no significant decreases in M_{max}-associated twitch forces during the 30 min after the interventions. Furthermore, the EMG-RMS amplitude during the training sets remained constant, suggesting that a compensatory increase in central drive was not needed to counteract reductions in muscle contractile properties or motoneuron excitability. Regarding central fatigue, although our data cannot discard the possibility of increased cortical inhibition, MEPs tended to remain depressed for more than 10 min when recorded at rest after fatiguing contractions (11). This depression contrasts with the increase in MEPs size and associated twitch forces for 25–30 min after RT ended (Figs. 4*A* and 5A). Also, if fatigue had affected motoneuron excitability, it would have reduced the responses to cervicomedullary electrical stimulation at rest (11), which is also in contrast with our findings. As a limitation to our study, we did not measure MVC after RT and, therefore, we cannot unequivocally rule out the effects of fatigue on the outcome measures.

Nonetheless, the acute changes in corticospinal response to a single bout of RT likely reflect initial neural adaptations to RT (27, 38) rather than a compensation for fatigue. Thus, our finding of a contraction intensity-dependent effect on cortical excitability could explain the absence of chronic neural adaptations (6, 13) (i.e., no changes in sEMG, V-wave, and voluntary activation) and the smaller MVC force increases that occur with low- compared with high-intensity RT (36).

Complementary Experiment

High- compared with low-exercise volume tends to produce greater increases in performance (26) and muscle mass (37). We found that a doubling of exercise volume increased MEP and associated twitch forces compared with the responses after the 25% intensity protocol without differences in CMEP size and associated twitch forces. Our data agree with a study reporting that training duration affected the involuntary twitch

responses generated by TMS toward the training direction after ballistic training (4). These results suggest that the volume of an acute isometric RT session of the elbow flexors also affected cortical excitability at rest in healthy men. However, we must be cautious with this conclusion because sample size was small in our complementary experiment.

Limitations

We did not match the size of MEPs and CMEPs, invalidating any comparisons between the two responses. However, as has been also argued (27), the time course of changes in MEP and CMEPs was different, with marked increases in MEP amplitude immediately after training in contrast to no changes in CMEPs at 10 min posttraining. Also, the larger baseline size of CMEPs (10% of M_{max}) could have reduced the potential for change. However, this is unlikely because CMEPs of larger baseline size (15–20% of M_{max}) increased to a greater extent after high-intensity RT (27) compared with the changes we observed. Future studies should match the size of MEPs and CMEPs, an approach that would make it possible to determine more accurately if the site of neural adaptation to RT is at the spinal or cortical level.

Conclusion

Collectively, our data tentatively suggest that the intensity of muscle contraction used in acute bouts of RT affects cortical excitability. The dose effects are probably related to the heightened cortical activation, resulting in greater adaptive processes in M1. Additionally, volume of acute RT also seems to contribute to the acute changes in cortical excitability. Future studies will determine whether there is a dose-response relationship between MVC force and neuronal excitability after chronic RT.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

D.C.-P., S.R.-A., T.H., and G.M. conceived and designed research; D.C.-P., S.R.-A., and G.M. performed experiments; D.C.-P. and G.M. analyzed data; D.C.-P., S.R.-A., J.L.-J., T.H., and G.M. interpreted results of experiments; D.C.-P. and G.M. prepared figures; D.C.-P., T.H., and G.M. drafted manuscript; D.C.-P., S.R.-A., J.L.-J., T.H., and G.M. edited and revised manuscript; D.C.-P., S.R.-A., J.L.-J., T.H., and G.M. approved final version of manuscript.

REFERENCES

1. **Aagaard P, Simonsen EB, Andersen JL, Magnusson P, Dyhre-Poulsen P.** Neural adaptation to resistance training: changes in evoked V-wave and H-reflex responses. *J Appl Physiol (1985)* 92: 2309–2318, 2002. doi:10.1152/japplphysiol.01185.2001.
2. **Akima H, Takahashi H, Kuno SY, Masuda K, Masuda T, Shimojo H, Anno I, Itai Y, Katsuta S.** Early phase adaptations of muscle use and strength to isokinetic training. *Med Sci Sports Exerc* 31: 588–594, 1999. doi:10.1097/00005768-199904000-00016.
3. **Bütefisch CM, Davis BC, Wise SP, Sawaki L, Kopylev L, Classen J, Cohen LG.** Mechanisms of use-dependent plasticity in the human motor cortex. *Proc Natl Acad Sci USA* 97: 3661–3665, 2000. doi:10.1073/pnas.97.7.3661.
4. **Classen J, Liepert J, Wise SP, Hallett M, Cohen LG.** Rapid plasticity of human cortical movement representation induced by practice. *J Neurophysiol* 79: 1117–1123, 1998. doi:10.1152/jn.1998.79.2.1117.
5. **Cohen JF.** Tests on Means in the Analysis of Variance and Covariance. In: *Statistical Power Analysis for the Behavioral Sciences,* edited by Cohen J. San Diego, CA: Academic, chap. 8, 1977, p. 273–406.
6. **Colomer-Poveda D, Romero-Arenas S, Vera-Ibáñez A, Viñuela-García M, Márquez G.** Effects of 4 weeks of low-load unilateral resistance training, with and without blood flow restriction, on strength, thickness, V wave, and H reflex of the soleus muscle in men. *Eur J Appl Physiol* 117: 1339–1347, 2017. doi:10.1007/s00421-017-3622-0.
7. **Collins BW, Cadigan EWJ, Stefanelli L, Button DC.** Corticospinal excitability of the biceps brachii is shoulder position dependent. *J Neurophysiol* 118: 3242–3251, 2017. doi:10.1152/jn.00527.2017.
8. **Dai TH, Liu JZ, Sahgal V, Brown RW, Yue GH.** Relationship between muscle output and functional MRI-measured brain activation. *Exp Brain Res* 140: 290–300, 2001. doi:10.1007/s002210100815.
9. **Delvendahl I, Kuhnke NG, Jung NH, Mainberger F, Cronjaeger M, Unterrainer J, Hauschke D, Mall V.** The time course of motor cortex plasticity after spaced motor practice. *Brain Stimul* 4: 156–164, 2011. doi:10.1016/j.brs.2010.10.002.
10. **Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, Mazzone P, Tonali P, Rothwell JC.** Effects of voluntary contraction on descending volleys evoked by transcranial stimulation in conscious humans. *J Physiol* 508: 625–633, 1998. doi:10.1111/j.1469-7793.1998.625bq.x.
11. **Gandevia SC, Petersen N, Butler JE, Taylor JL.** Impaired response of human motoneurones to corticospinal stimulation after voluntary exercise. *J Physiol* 521: 749–759, 1999. doi:10.1111/j.1469-7793.1999.00749.x.
12. **Giboin LS, Weiss B, Thomas F, Gruber M.** Neuroplasticity following short-term strength training occurs at supraspinal level and is specific for the trained task. *Acta Physiol (Oxf)* 222: e12998, 2018.
13. **Jenkins NDM, Miramonti AA, Hill EC, Smith CM, Cochrane-Snyman KC, Housh TJ, Cramer JT.** Greater neural adaptations following high- vs. low-load resistance training. *Front Physiol* 8: 331, 2017. doi:10.3389/fphys.2017.00331.
14. **Jensen JL, Marstrand PC, Nielsen JB.** Motor skill training and strength training are associated with different plastic changes in the central nervous system. *J Appl Physiol (1985)* 99: 1558–1568, 2005. doi:10.1152/japplphysiol.01408.2004.
15. **Kamen G, Knight CA.** Training-related adaptations in motor unit discharge rate in young and older adults. *J Gerontol A Biol Sci Med Sci* 59: 1334–1338, 2004. doi:10.1093/gerona/59.12.1334.
16. **Koo TK, Li MY.** A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med* 15: 155–163, 2016. [Erratum in *J Chiropr Med* 15: 155–163, 2016]. 2017] doi:10.1016/j.jcm.2016.02.012.
17. **Latella C, Hendy A, Vanderwesthuizen D, Teo WP.** The modulation of corticospinal excitability and inhibition following acute resistance exercise in males and females. *Eur J Sport Sci* 18: 984–993, 2018. doi:10.1080/17461391.2018.1467489.
18. **Latella C, Teo WP, Harris D, Major B, VanderWesthuizen D, Hendy AM.** Effects of acute resistance training modality on corticospinal excitability, intra-cortical and neuromuscular responses. *Eur J Appl Physiol* 117: 2211–2224, 2017. doi:10.1007/s00421-017-3709-7.
19. **Leung M, Rantalainen T, Teo WP, Kidgell D.** Motor cortex excitability is not differentially modulated following skill and strength training. *Neuroscience* 305: 99–108, 2015. doi:10.1016/j.neuroscience.2015.08.007.
20. **Lundbye-Jensen J, Petersen TH, Rothwell JC, Nielsen JB.** Interference in ballistic motor learning: specificity and role of sensory error signals. *PLoS One* 6: e17451, 2011. doi:10.1371/journal.pone.0017451.
21. **Martin PG, Gandevia SC, Taylor JL.** Output of human motoneuron pools to corticospinal inputs during voluntary contractions. *J Neurophysiol* 95: 3512–3518, 2006. doi:10.1152/jn.01230.2005.
22. **Mason J, Frazer AK, Pearce AJ, Goodwill AM, Howatson G, Jaberzadeh S, Kidgell DJ.** Determining the early corticospinal-motoneuronal responses to strength training: a systematic review and meta-analysis. *Rev Neurosci* 30: 463–476, 2019. doi:10.1515/revneuro-2018-0054.

23. **Moritani T, deVries HA.** Neural factors versus hypertrophy in the time course of muscle strength gain. *Am J Phys Med* 58: 115–130, 1979.
24. **Muddle TWD, Colquhoun RJ, Magrini MA, Luera MJ, DeFreitas JM, Jenkins NDM.** Effects of fatiguing, submaximal high- versus low-torque isometric exercise on motor unit recruitment and firing behavior. *Physiol Rep* 6: e13675, 2018. doi:10.14814/phy2.13675.
25. **Muellbacher W, Ziemann U, Boroojerdi B, Cohen L, Hallett M.** Role of the human motor cortex in rapid motor learning. *Exp Brain Res* 136: 431–438, 2001. doi:10.1007/s002210000614.
26. **Munn J, Herbert RD, Hancock MJ, Gandevia SC.** Resistance training for strength: effect of number of sets and contraction speed. *Med Sci Sports Exerc* 37: 1622–1626, 2005. doi:10.1249/01.mss.0000177583.41245.f8.
27. **Nuzzo JL, Barry BK, Gandevia SC, Taylor JL.** Acute strength training increases responses to stimulation of corticospinal axons. *Med Sci Sports Exerc* 48: 139–150, 2016. doi:10.1249/MSS.0000000000000733.
28. **Nuzzo JL, Barry BK, Jones MD, Gandevia SC, Taylor JL.** Effects of four weeks of strength training on the corticomotoneuronal pathway. *Med Sci Sports Exerc* 49: 2286–2296, 2017. doi:10.1249/MSS.0000000000001367.
29. **Nuzzo JL, Trajano GS, Barry BK, Gandevia SC, Taylor JL.** Arm posture-dependent changes in corticospinal excitability are largely spinal in origin. *J Neurophysiol* 115: 2076–2082, 2016. doi:10.1152/jn.00885.2015.
30. **Ortu E, Deriu F, Suppa A, Tolu E, Rothwell JC.** Effects of volitional contraction on intracortical inhibition and facilitation in the human motor cortex. *J Physiol* 586: 5147–5159, 2008. doi:10.1113/jphysiol.2008.158956.
31. **Perez MA, Cohen LG.** Scaling of motor cortical excitability during unimanual force generation. *Cortex* 45: 1065–1071, 2009. doi:10.1016/j.cortex.2008.12.006.
32. **Perez MA, Lungholt BK, Nyborg K, Nielsen JB.** Motor skill training induces changes in the excitability of the leg cortical area in healthy humans. *Exp Brain Res* 159: 197–205, 2004. doi:10.1007/s00221-004-1947-5.
33. **Rodriguez-Falces J, Place N.** Determinants, analysis and interpretation of the muscle compound action potential (M wave) in humans: implications for the study of muscle fatigue. *Eur J Appl Physiol* 118: 501–521, 2018. doi:10.1007/s00421-017-3788-5.
34. **Rogasch NC, Dartnall TJ, Cirillo J, Nordstrom MA, Semmler JG.** Corticomotor plasticity and learning of a ballistic thumb training task are diminished in older adults. *J Appl Physiol (1985)* 107: 1874–1883, 2009. doi:10.1152/japplphysiol.00443.2009.
35. **Ruotsalainen I, Ahtiainen JP, Kidgell DJ, Avela J.** Changes in corticospinal excitability during an acute bout of resistance exercise in the elbow flexors. *Eur J Appl Physiol* 114: 1545–1553, 2014. doi:10.1007/s00421-014-2884-z.
36. **Schoenfeld BJ, Grgic J, Ogborn D, Krieger JW.** Strength and hypertrophy adaptations between low- versus high-load resistance training: A systematic review and meta-analysis. *J Strength Cond Res* 31: 3508–3523, 2017. doi:10.1519/JSC.0000000000002200.
37. **Schoenfeld BJ, Ogborn D, Krieger JW.** Dose-response relationship between weekly resistance training volume and increases in muscle mass: A systematic review and meta-analysis. *J Sports Sci* 35: 1073–1082, 2017. doi:10.1080/02640414.2016.1210197.
38. **Selvanayagam VS, Riek S, Carroll TJ.** Early neural responses to strength training. *J Appl Physiol (1985)* 111: 367–375, 2011. doi:10.1152/japplphysiol.00064.2011.
39. **Todd G, Taylor JL, Gandevia SC.** Reproducible measurement of voluntary activation of human elbow flexors with motor cortical stimulation. *J Appl Physiol (1985)* 97: 236–242, 2004. doi:10.1152/japplphysiol.01336.2003.
40. **Ugawa Y, Terao Y, Hanajima R, Sakai K, Kanazawa I.** Facilitatory effect of tonic voluntary contraction on responses to motor cortex stimulation. *Electroencephalogr Clin Neurophysiol* 97: 451–454, 1995. doi:10.1016/0924-980X(95)00214-6.
41. **Weavil JC, Sidhu SK, Mangum TS, Richardson RS, Amann M.** Intensity-dependent alterations in the excitability of cortical and spinal projections to the knee extensors during isometric and locomotor exercise. *Am J Physiol Regul Integr Comp Physiol* 308: R998–R1007, 2015. doi:10.1152/ajpregu.00021.2015.
42. **Ziemann U, Muellbacher W, Hallett M, Cohen LG.** Modulation of practice-dependent plasticity in human motor cortex. *Brain* 124: 1171–1181, 2001. doi:10.1093/brain/124.6.1171.

ANNEX 4: Study 2. Reference: Colomer-Poveda D, Romero-Arenas S, Keller M, Hortobagyi T, Marquez G. Effects of acute and chronic unilateral resistance training variables on ipsilateral motor cortical excitability and cross-education: A systematic review. Physical therapy in sport: official journal of the Association of Chartered Physiotherapists in Sports Medicine. 2019;40:143-52. doi: 10.1016/j.ptsp.2019.09.006.

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Literature Review

Effects of acute and chronic unilateral resistance training variables on ipsilateral motor cortical excitability and cross-education: A systematic review

D. Colomer-Poveda [a], S. Romero-Arenas [a], M. Keller [b], T. Hortobágyi [c], G. Márquez [a, *]

[a] Department of Physical Education and Sport, Faculty of Sport, Catholic University of Murcia (UCAM), Murcia, Spain
[b] Department of Sport, Exercise and Health, University of Basel, Basel, Switzerland
[c] Center for Human Movement Sciences, University of Groningen, University Medical Center Groningen, Groningen, Netherlands

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ABSTRACT

Objective: The increase in voluntary force of an untrained limb (i.e. Cross-education) after unilateral resistance training (RT) is believed to be a consequence of cortical adaptations. However, studies measuring neurophysiological adaptations with transcranial magnetic stimulation (TMS) found inconsistent results. One unexamined factor contributing to the conflicting data is the variation in the type and intensity of muscle contractions, fatigue, and the strategies of pacing the movement. Therefore, the purpose was to analyse how those unilateral RT variables affect the adaptations in ipsilateral M1 (iM1) and cross-education.
Methods: We performed a systematic literature review, with the following search terms with Boolean conjunctions: "Transcranial magnetic stimulation" AND "Ipsilateral cortex" AND "Resistance training".
Results: The 11 acute and 12 chronic studies included partially support the idea of increased cortical excitability and reduced intracortical inhibition in iM1, but the inconsistency between studies was high.
Conclusions: Differences in type and intensity of contraction, fatigue, and strategies of pacing the movement contributed to the inconsistencies. The tentative conclusion is that high intensity eccentric or externally paced contractions are effective to increase iM1 excitability but cross-education can occur in the absence of such changes. Thus, the mechanism of the cross-education examined with TMS remains unclear.

1. Introduction

Unilateral muscle contractions activate contralateral but also ipsilateral brain structures (Dai, Liu, Sahgal, Brown, & Yue, 2001). Such ipsilateral brain activation occurs during the execution of simple motor skills requiring little effort and parametrically increases with the intensity of isometric and dynamic muscle contraction (Muellbacher, Facchini, Boroojerdi, & Hallett, 2000; Perez and Cohen, 2008, 2009). However, the source of this ipsilateral brain activation is not entirely clear. Because the delay between the activation in the two hemispheres is in the millisecond range, a part of the activation is likely to occur simultaneously and inadvertently, while there is a temporal element of this activation that is due to interhemispheric actions acting on intracortical circuits in the ipsilateral hemisphere (Kristeva, Cheyne, & Deecke, 1991).

Short-term unilateral resistance training (RT) produces not only increases in voluntary muscle force of the trained muscle but also in the non-practice homologous muscle, a phenomenon known as cross-education (Munn, Herbert, & Gandevia, 2004). Although short-term motor skill training also leads to interlimb transfer of skill (Perez et al., 2007; Schulze, Luders, & Jancke, 2002), the present review focuses only on the cross-education of voluntary muscle force. Typically, cross-education is muscle-specific but without (or little) peripheral adaptations in the untrained muscle itself (Narici, Roi, Landoni, Minetti, & Cerretelli, 1989). By default, cross-education after unilateral RT was assumed to have a neural origin (Lee & Carroll, 2007). At least two neural mechanisms can (partly) explain cross-education after unilateral RT. One is related to the possibility that the repeated activation of the ipsilateral brain structures by the unilateral muscle contractions during unilateral

* Corresponding author. Facultad de Deporte - Universidad Católica de Murcia, Campus de los Jerónimos s/n. Guadalupe, 30107, Murcia, Spain.
E-mail address: gmarquez@ucam.edu (G. Márquez).

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RT serves as the training stimulus for adaptations in the ipsilateral brain areas. Such a mechanism is supported by the increase in the number of corticospinal neurons recruited in the untrained limb (Hortobagyi et al., 2011; Kidgell et al., 2015; Mason et al., 2017) and reductions in intracortical inhibition (Coombs et al., 2016; Latella, Kidgell, & Pearce, 2012; Leung, Rantalainen, Teo, & Kidgell, 2018; Zult et al., 2016). In other words, cross-activation during unilateral contractions leads to neuroplastic changes in both cortices (Lee & Carroll, 2007; Ruddy & Carson, 2013) that increase the output produced by the motor command, potentially explaining behavioural gains in the untrained limb. A second potential mechanism is an altered interhemispheric communication after unilateral RT (Hortobagyi et al., 2011) that can also influence short intracortical inhibition (SICI) and long intracortical inhibition (LICI) circuits in the transfer hemisphere (Perez & Cohen, 2008) and, thus, be the basis for cross-education.

However, despite the solid theoretical foundation for this hypothesis, there are many inconsistencies in the effects of acute or chronic unilateral RT on iM1 excitability quantified by ipsilateral CSE, ipsilateral intracortical inhibition, and ipsilateral facilitation, making it difficult to determine the neural mechanisms underlying cross-education. It is possible that the inconsistencies are due to the differences between studies with respect to training variables such as the intensity (Muellbacher et al., 2000) and the type of muscle contraction (Howatson et al., 2011), the degree of fatigue, and the external pacing of muscle contraction (Leung, Rantalainen, Teo, & Kidgell, 2015), which can affect the adaptations in iM1. Thus, it is probably that those training variables per se affect the acute and chronic adaptations in iM1 excitability, and hence cross-education.

Therefore, the purpose of this review is to determine the effects of the type of muscle contraction, the training intensity, the degree of fatigue and the external pacing of muscle contractions on iM1 adaptations. Also to determine if iM1 adaptations are related to the effectiveness of the motor command, producing correlated increases in cross-education following acute and chronic unilateral RT in healthy adults.

2. Methods

The present systematic review was performed according to the 'Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols' (PRISMA-P) 2015 guidelines (Moher et al., 2015).

2.1. Search strategy

A systematic literature review included papers published between January 1950 and March 2018 in the online databases MEDLINE (via PubMed) and Web of Science. The main search terms were "Transcranial magnetic stimulation", AND "Ipsilateral cortex", AND "Resistance training", and its synonyms. Tracking of cited studies and hand searching of relevant articles were also completed. The literature search was conducted by DCP. The authors were contacted to provide the data missing from original papers but needed for the review.

2.2. Eligibility criteria and study selection

After removal of duplicates, the remaining studies were screened manually based on title, abstract, and full-text. To guide the exclusion and inclusion criteria we followed the PICOS guidelines (Population, Intervention, Comparator, Outcomes, and Study) (Harris, Quatman, Manring, Siston, & Flanigan, 2014).The following PICOS criteria were applied. (i) Population: healthy adults (free of orthopaedic and neurological conditions) age 18–55 years. (ii) Intervention: Unilateral RT session was considered as a unilateral repetitive task at a given percent of repetition maximum (RM), absolute load (Kg), if the task was dynamic, or percent MVC, if the task was isometric, while the other limb was at rest. Duration of unilateral RT was defined as a minimum of two sessions per week for at least two weeks for the chronic studies. (iii) Comparator: For chronic studies, a control group that did receive no intervention or a no-intervention control period for the experimental group served as comparators. For acute studies, not control intervention was required. (iv) Outcomes: Adaptations in the iM1 had to be measured with TMS using different stimulation protocols. At least one of the following outcome parameters measured in iM1 was necessary for inclusion of the respective study: motor evoked potential (MEP) amplitude, SICI, interhemispheric inhibition, ICF or contralateral silent period (cSP) before and after unilateral RT. (v) Study: randomized trial were included.

Studies were excluded that used sustained unilateral muscle contractions to fatigue or to a time limit, used electrical muscle stimulation, or direct/placebo stimulation of the corticospinal tract (EMS, a-tDCS, PAS, rTMS …). A consensus among three of the authors (DCP, GM and TH) guaranteed that the studies included in the review met the inclusion.

2.3. Coding

We coded the data for authors, publication date, sample size, participants' characteristics (age, limb dominance), muscle group trained, details of resistance training intervention (duration, sessions, volume, intensity, exercise type), key outcome (TMS measurements and strength measures for case of chronic studies), and results of the study regarding the key outcomes.

2.4. Assessment of methodological quality

We computed the PEDro score to assess the methodological quality of the included studies (Maher, Sherrington, Herbert, Moseley, & Elkins, 2003). The scale consists of 11 criteria, of which the first is not included in the total score. Each criterion is rated "yes" or "no," and a "yes" should only be awarded when a criterion is clearly satisfied. If all criteria are satisfied, the maximum score of 10 can be given. Included studies with a PEDro score of ≥6/10 were considered of high quality, whereas a score of 5/10 or lower was considered as low methodological quality. Two researchers (DCP, SRA) independently assessed the methodological quality and discrepancies were resolved by discussion until consensus was reached. Additionally we also assessed the methodological quality of the acute studies without control group using the 'Quality assessment tool for before-after studies with no control group' (National Heart La and Nati, 2014), a 12-question tool which rates the methodological quality of the studies as "good", "fair" or "poor" (7 studies). The raters were not blinded to study authors, place of publication, and results.

3. Results

3.1. Search results

Fig. 1 shows the flow diagram of the systematic review. The search identified 687 studies. After duplicates, 518 studies were left. After checking the titles, abstracts, and the full-text as needed, 22 studies met the inclusion criteria, 11 to analyse the acute effects, and 12 studies to analyse for chronic effects (one study was included in both analysis).

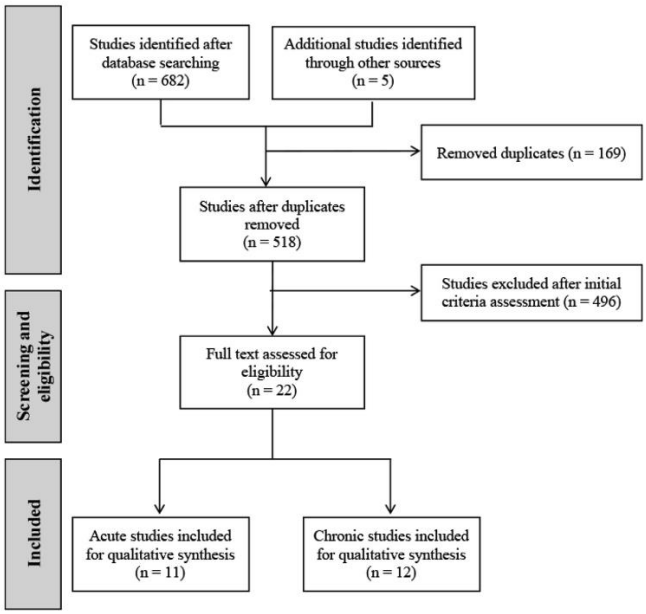

Fig. 1. Flow diagram of studies identified, excluded, and included in the systematic review.

3.2. Quality assessment

Tables 1 and 2 show the quality scores. 75% of the studies revealed a high quality PEDro score (≥6 points). The methodological quality of the before-after studies without a control group was "fair".

3.3. Participants and study characteristics

3.3.1. Acute studies

Table 1 summarize the study characteristics using dynamic and isometric muscle contraction as a training stimulus. The 11 studies were published between 2002 and 2015. The sample size per study ranged between eight and 32 (mean 15.4, total N = 174), and participants' age was 19–55 years. Two of the 11 studies reported subjects' training status, with one including a mix of sedentary, endurance, and resistance-trained participants (Triscott et al., 2008), and the other including subjects with no experience in strength training of the fingers (Hortobagyi et al., 2011). Most participants were right handed, whereas in four studies there were both, right and left handed subjects (total of 11 left handed subjects) (Goodall et al., 2013; Leung et al., 2015; Schmidt, Hinder, Summers, & Garry, 2011; Triscott et al., 2008).

All but one study (Lagerquist, Mang, & Collins, 2012) trained an upper extremity muscle. Participants trained the dominant (n = 7 studies) (Goodall et al., 2013; Gorsler, Zittel, Weiller, Munchau, & Liepert, 2004; Hortobagyi et al., 2011; Humphry et al., 2004; Lagerquist et al., 2012; Schmidt et al., 2011; Triscott et al., 2008) or the non-dominant limb (n = 4 studies) (Baumer, Munchau, Weiller, & Lieper, 2002; Edgley & Winter 2004; Leung et al., 2015; Takahashi et al., 2009). Studies included dynamic (Edgley & Winter 2004; Humphry et al., 2004; Leung et al., 2015; Triscott et al., 2008) and static (Baumer et al., 2002; Goodall et al., 2013; Gorsler et al., 2004; Hortobagyi et al., 2011; Lagerquist et al., 2012; Schmidt et al., 2011; Takahashi et al., 2009) muscle contractions. Five studies included at least one situation in which the specified training was performed until they could no longer complete the movement (Edgley & Winter 2004; Humphry et al., 2004; Triscott et al., 2008), achieve the desired force level (Baumer et al., 2002) or even until they could no longer exert any force (complete exhaustion) (Takahashi et al., 2009). In eight studies, there was at least one intervention without an explicit intention to perform contractions until complete exhaustion (Goodall et al., 2013; Gorsler et al., 2004; Hortobagyi et al., 2011; Lagerquist et al., 2012; Leung et al., 2015; Schmidt et al., 2011). Regarding training intensity, six studies used low intensity contractions (1%–30% of 1RM or MVC) (Baumer et al., 2002; Edgley & Winter 2004; Gorsler et al., 2004; Humphry et al., 2004; Lagerquist et al., 2012; Triscott et al., 2008), four studies used medium intensity (31–60% of 1RM or MVC) (Baumer et al., 2002; Goodall et al., 2013; Schmidt et al., 2011; Takahashi et al., 2009), and two studies used high intensity contractions (>61% of 1RM or MVC) (Hortobagyi et al., 2011; Leung et al., 2015).

3.3.2. Chronic studies

Table 2 summarize chronic studies, published between 2011 and 2018 using dynamic or isometric contractions during training. The studies used a pre-post design, with all but one study including a no-intervention control group or control period (Zult et al., 2016).

Table 1
Acute effects of 1 session of dynamic ($n = 4$) and static ($n = 7$) resistance training on ipsilateral TMS measurements.

Study	Sample	Muscle group	Intervention		Neurophysiological measures	Main outcomes	Quality
Baumer et al. (2002)	n = 10 (all RHD) Age range: 27–38 yrs Gender: All ♂	Right FDI	Experiment 1: Left hand repetitive pinch grips (1 −2 Hz) of 50% of MVC, until the inability to reach the required force level.		CSE, SICI, and ICF at rest	CSE and SICI: ↔ ICF: ↓* 96% after 2–6 min ↔ after 15 −19 min	Fair
			Experiment 2: Same intervention (same volume) without fatigue with 5% MVC contractions.		CSE, SICI, and ICF at rest	CSE, SICI, and ICF: ↔	
Edgley and Winter (2004)	n = 9 (all RHD) Age range: 21–42 yrs Gender: 4♀; 5♂	Right FDI	Left pinch grips against spring-loaded levers separated by 10 cm until subjects were unable to close levers.		CSE and IHI during contraction	CSE and IHI: ↔	Fair
Gorsler et al. (2004)	n = 20 (all RHD) Age range: 20–39 yrs Gender: All ♂	Left FDI	30 min of right handed pinch grips of 2% of MVC every 3 s		CSE and 6 m s ISI paired pulse stimulation during contraction	CSE: ↔ Facilitation of paired pulse stimulation (6 m s ISI) during trained limb contraction was ↓*	Fair
Humphry et al. (2004)	n = 8 (all RHD) Age range: 19–25 yrs Gender: 1♀; 6♂	Left BB	Elbow flexions against 3.5 kg at a frequency of 1 Hz.	Experiment 1: Until exhaustion	CSE at rest	↓* 60.6 ± 4.9% after 10–18 min. ↔ after 40 min	Fair
				Experiment 2: Until 25% of time to exhaustion	CSE at rest	↔ Just after. ↑* 166.5 ± 4.6% after 10 min–60 min.	
Triscott et al. (2008)	n = 24 (19 RHD, 5 LHD) Age range: 20–57 yrs Gender: 3♀; 21♂	Dominant BB	Non-dominant elbow flexions against 4.5 kg until exhaustion	Sedentary subjects (n = 8)	CSE at rest	↓* 38-27% during the first 20 min	Fair
				Resistance trained subjects (n = 8)	CSE at rest	↓* 53-26% during the first 30 min	
				Endurance trained subjects (n = 8)	CSE at rest	↓* 47-38% during the first 10 min	
Takahashi et al. (2009)	n = 17 (all RHD) Age range: 21–24 yrs Gender: All ♂	Right FDI	Repeated left hand grips of 50% (1 Hz) of MVC until complete exhaustion		CSE, SICI, and ICF at rest.	CSE: ↔ immediately after, ↓* 15% from 5 to 15 min after. SICI: ↓* 57% from 5 to 15 min after. ICF: ↔	Fair
Hortobagyi et al. (2011)	n = 20 (all RHD) Age range: 30.9 ± 1.4 yrs Gender: 8♀; 12♂	Right FDI	Intervention group (n = 12): 5 sets × 10 reps at 80% of MVC of isometric index finger abduction. Tempo: 5″ contraction − 5″ rest		CSE, SICI, IHI, and ICF at rest.	CSE, SICI, and ICF: ↔ IHI: ↓* 8.9%	6
			Control group (n = 8): Without training		CSE, SICI, IHI, and ICF at rest.	CSE, SICI, and ICF: ↔ IHI: ↓* 1.8%	
Schmidt et al. (2011)	n = 11 (9 RHD, 2 LHD) Age: 27.3 ± 7.8 yrs Gender: 4♀; 7♂	Left FDI	10 sets × 50 reps of isometric right thumb abductions of an intensity of 35% of MVC paced with a temporal target (0.5 Hz)		CSE, SICI, and ICF at rest.	CSE and SICI: ↔ ICF: ↓* 27.3% immediately after training	Fair
Lagerquist et al. (2012)	n = 10 (all RHD) Age range: 22–44 yrs Gender: 3♀; 7♂	Left Soleus	Voluntary isometric contractions at 20% of MVC (5″ contraction − 5″ rest) for 40 min		CSE during contraction	CSE: ↔	6
			Control condition with no training		CSE during contraction	CSE: ↔	
Goodall et al. (2013)	n = 13 (12 RHD, 1 LHD) Age: 40 ± 12 yrs Gender: 3♀; 10♂	Non-dominant FPB	15 min of intermittent isometric pinch task at 35% of MVC (5″ contraction − 5″ rest).		CSE at rest	CSE: ↔	6
			Control condition with no training		CSE at rest	CSE: ↔	
Leung et al. (2015)	n = 32 (29 RHD, 3 LHD) Age: 26.1 ± 6.8 yrs Gender: 20♀; 24♂	Non-dominant BB	Metronome paced (n = 11): Dominant elbow flexion: 4 sets × 6–8 reps at 70 −80% of 1-RM. Tempo: 3 s concentric − 4 s eccentric		CSE and SICI during contraction	CSE: ↑* 43.3 ± 4.9% SICI: ↓* 20.3 ± 4.6%	6
			Self-paced (n = 11): Dominant elbow flexion: 4 sets × 6–8 reps at 70 −80% of 1-RM. Tempo: Preferred tempo		CSE and SICI during contraction	CSE and SICI: ↔	
			Control group (n = 10): Without training		CSE and SICI during contraction	CSE and SICI: ↔	

*Statistically significant change $P < 0.05$; RHD: Right hand dominant; LHD: Left hand dominant; BB: Biceps brachialis; FDI: First dorsal digitorum; FPB: Flexor policis brevis; MVC: Maximal voluntary contraction; CSE: Corticospinal excitability; IHI: Interhemispheric inhibition; SICI: Short interval intracortical inhibition; ICF: Intracortical facilitation; ISI: Interstimulus interval.

Table 2
Chronic effects of dynamic ($n = 10$) and static ($n = 2$) resistance training on ipsilateral TMS measurements and untrained limb strength.

Study	Sample	Muscle group	Intervention	Neurophysiological measures	Main outcomes	Δ strength of untrained limb	Quality
Hortobagyi et al. (2011)	n = 20 (all RHD) Age: 30.9 ± 1.4 yrs Gender: 8♀; 12♂	Right FDI	Intervention group (n = 12): 8 weeks, 20 sessions of 5 sets × 10 reps at 80% of MVC of isometric index finger abduction. Tempo: 5″ contraction − 5″ rest	CSE, SICI, IHI, and ICF at rest, and during trained limb contraction	CSE: ↑* 6% at rest and ↑* 10%, or 64% during trained limb contraction of 20 or 80% of MVC, respectively. SICI: ↔ ICF: ↔ IHI: ↓* 31%	↑* 21.8 ± 2.3%	
			Control group (n = 8): Without training	CSE, SICI, IHI, and ICF at rest, and during trained limb contraction	CSE: ↔ SICI: ↔ ICF: ↔ IHI: ↔	↔	
Kidgell et al. (2011)	n = 23 (all RHD) Age: 22.4 yrs Gender: 10♀; 13♂	Right BB	Intervention group (n = 13): 4 weeks, 12 sessions of 4 sets × 6–8 reps at 80% of 1-RM of unilateral dynamic elbow flexion. Tempo: 3″ concentric − 4″ eccentric	CSE and SP during contraction	CSE: ↑* 33% SP: ↔	↑* 19.2% (11.3 ± 4.9 Kg to 13.7 ± 5.4 Kg)	6
			Control group (n = 10): Control period without training	CSE and SP during contraction	CSE and SP: ↔	↔	
Goodwill et al. (2012)	n = 14 (all RLD) Age: 21 ± 1.1 yrs Gender: 7♀; 7♂	Right RF	Intervention group (n = 7): 3 weeks, 9 sessions of 4 sets × 6–8 reps at 75%–80% of 1-RM of single leg squats. Tempo: 3″ concentric − 4″ eccentric	CSE during contraction and SICI at rest	CSE: ↑* 32% SICI: ↓* 24.56%	↑* 35.4%	6
			Control group (n = 7): Control period without training	CSE during contraction and SICI at rest	CSE and SICI: ↔	↔	
Goodwill et al. (2012)	n = 14 (all RLD) Age: 21 ± 1.1 yrs Gender: 7♀; 7♂	Right RF	Intervention group (n = 7): 3 weeks, 9 sessions of 4 sets × 6–8 reps at 75%–80% of 1-RM of single leg squats. Tempo: 3″ concentric − 4″ eccentric	CSE during contraction and SICI at rest	CSE: ↑* 62.3% SICI: ↓* 21.3%	↑* 35.4%	6
			Control group (n = 7): Control period without training	CSE during contraction and SICI at rest	CSE and SICI: ↔	↔	
Latella et al. (2012)	n = 18 (all RLD) Age range: 18–35 yrs Gender: 4♀; 14♂	Right RF	Intervention group (n = 9): 8 weeks, 24 sessions of 3 sets × 4–8 reps progressed from 78 to 88.5% of 1-RM (single leg press). Tempo: Unknown	CSE and SP during contraction	CSE: ↔ SP: ↓* 18%	↑* 20.4%	4
			Control group (n = 9): Control period without training	CSE and SP during contraction	CSE and SP: ↔	↔	
Kidgell et al. (2015)	n = 27 (all RHD) Age: 26 ± 1.5 yrs Gender: 12♀; 15♂	Right FCR	Eccentric group (n = 9): 4 weeks, 12 sessions of 4 sets × 6–8 reps of maximal eccentric wrist flexions at 0.34 rad s^{-1}	CSE, SP, and SICI during isometric, eccentric and concentric contractions	CSE during eccentric contractions: ↑* 51%, and ↔ during isometric and concentric contractions SICI during isometric contraction: ↓* 32% SP during isometric contraction: ↓* 27% SP and SICI during concentric and eccentric contractions: ↔	Isometric: ↑* 43% Eccentric: ↑* 47% Concentric: ↑* 49%	6
			Concentric group (n = 9): 4 weeks, 12 sessions of 4 sets × 6–8 reps of maximal concentric wrist flexions at 0.34 rad s^{-1}	CSE, SP, and SICI during isometric, eccentric, and concentric contractions	CSE, SP, and SICI during isometric, concentric, and eccentric contractions: ↔	Isometric: ↔ Eccentric: ↔ Concentric: ↑* 28%	
			Control group (n = 9): Control period without training	CSE, SP, and SICI during isometric, eccentric, and concentric contractions	CSE, SP, and SICI during isometric, concentric, and eccentric contractions: ↔	Isometric: ↔ Eccentric: ↔ Concentric: ↔	
Urbin et al. (2015)	n = 4 (3 RHD, 1 LHD) Age: 50 ± 11.8 yrs Gender: 3♀; 1♂	Right and left EDC	Intervention period (n = 4): 4 weeks, 16 sessions of 6 sets × 6–8 reps at 80% of 1-RM of dynamic wrist extension. Tempo: 3″ concentric − 4″ eccentric	CSE and SP during contraction	CSE and SP: ↔	↑* 19% (from 10.5 Kg to 12.5 Kg)	1
			Control period (n = 4): 4 weeks without training just before training intervention	CSE and SP during contraction	CSE and SP: ↔	↔	
Coombs et al. (2016)	n = 23 (all RHD) Age range: 18–36 yrs Gender: 12♀; 11♂	Right or Left ECR	Right hand training group (n = 8): 3 weeks, 9 sessions of 4 sets × 6–8 reps at 70% of 1-RM of dynamic extension of wrist (with dumbbell).Tempo: 3″ concentric − 4″ eccentric	CSE, SICI, and SP during contraction	CSE and SICI: ↔ SP: ↓* 14–27%	↑*10% (from 7.90 ± 2.90 Kg to 8.74 ± 3.10 Kg)	7
			Left hand training group (n = 8): 3 weeks, 9 sessions of 4 sets × 6–8 reps at 70% of 1-RM of dynamic extension of wrist (with dumbbell).Tempo: 3″ concentric − 4″ eccentric	CSE, SICI, and SP during contraction	CSE, SICI, and SP: ↔	↑* 15% (from 8.80 ± 2.70 Kg to 10.20 ± 3.60 Kg)	
			Control group (n = 7): Control period without training	CSE, SICI, and SP during contraction	CSE, SICI, and SP: ↔	↔	

(continued on next page)

Table 2 (*continued*)

Study	Sample	Muscle group	Intervention	Neurophysiological measures	Main outcomes	Δ strength of untrained limb	Quality
Manca et al. (2016)	n = 34 (all RHD); Age: 25.5 ± 6.0yrs Gender: 11♀; 23♂	Right FDI	Intervention group (n = 17): 4 weeks; 12 sessions of 5 sets × 10 reps of MVC of isometric key pinching. Tempo: 5″ contraction − 5″ rest	CSE, SICI, ICF, and IHI at rest	CSE, SICI, ICF, and IHI: ↔	↑* 7.7% (from 20.6 ± 4.2 Kg to 22.2 ± 4.6 Kg)	6
			Control group (n = 17): Without training	CSE, SICI, ICF, and IHI at rest	CSE, SICI, ICF, and IHI: ↔	↔	
Zult et al. (2016)	n = 24 (all RHD) Age: 27 ± 10 yrs Gender: 5♀; 19♂	Right FCR	Non mirror training group (n = 12): 3 weeks, 15 sessions of 6 sets × 8 reps at 80% of MVC of dynamic wrist flexions without any visual feedback of the untrained wrist. Tempo: Unknown	CSE, SICI, SP, and IHI at rest, and during trained limb contraction	CSE and SICI at rest: ↔ CSE during trained limb contraction: ↑*49–55% SICI during trained limb contraction: ↓* 28–45% SP: ↔ IHI: ↓* 15%	↑* 34% (from 9.0 ± 3.0 N m to 14.4 ± 2.5 N m)	6
			Mirror training group (n = 12): 3 weeks, 15 sessions of 6 sets × 8 reps at 80% of MVC of dynamic wrist flexions with mirror visual feedback of the untrained wrist. Tempo: Unknown	CSE, SICI, SP, and IHI at rest, and during trained limb contraction	CSE and SICI at rest: ↔ CSE during trained limb contraction: ↑*49–55% SICI during trained limb contraction: ↓* 28–45% SP: ↓* 15% IHI: ↑* 11	↑* 61% (from 9.5 ± 3.7 N m to 12.7 ± 4.4 N m)	
Mason et al. (2017)	n = 10 (all RHD) Age range: 18–35 yrs Gender: 10♀; 10♂	Right BB	Intervention group (n = 10): 3 weeks, 9 sessions of 4 sets × 6–8 reps at 80% of 1-RM of unilateral dynamic elbow flexion. Tempo: 3″ concentric − 4″ eccentric	CSE and SP during contraction	CSE: ↑* 25% SP: ↓* 15.3%	↑* 23%	7
		Right BB	Control group (n = 10): Control period without training	CSE and SP during contraction	CSE and SP: ↔	↔	
Leung et al. (2018)	n = 32 (3 LHD, 29 RHD) Age: 26.4 ± 6.9 yrs Gender: 17♀; 15♂	Dominant BB	Metronome paced group (n = 11): 4 weeks, 12 sessions of 4 sets × 6–8 reps at 80% of 1-RM of unilateral dynamic elbow flexion. Tempo: 3″ concentric − 4″ eccentric	CSE and SICI during contraction	CSE: ↑* 106% SICI: ↓* 47%	↑* 16%	6
			Self-paced group (n = 11): 4 weeks, 12 sessions of 4 sets × 6–8 reps at 80% of 1-RM of unilateral dynamic elbow flexion. Preferred tempo	CSE and SICI during contraction	CSE and SICI: ↔	↑* 13%	
			Control group (n = 10): Control period without training	CSE and SICI during contraction	CSE and SICI: ↔	↔	

* Statistically significant change $P < 0.05$; RHD: Right hand dominant; LHD: Left hand dominant; RLD: Right leg dominant; BB: Biceps brachialis; RF: Rectus femoris; FCR: Flexor carpi radialis; EDC: Extensor digitorum communis; ECR: Extensor carpi radialis FDI: First dorsal digitorum; RM: Repetition maximum; MVC: Maximum voluntary contraction; CSE: Corticospinal excitability; IHI: Interhemispheric inhibition; SICI: Short interval intracortical inhibition; ICF: Intracortical facilitation; SP: Silent period.

The sample size ranged from four (Urbin, Harris-Love, Carter, & Lang, 2015) to 34 (Manca et al., 2016) subjects (mean 21.08 ± 8.2, n = 253). Participants were untrained (Coombs et al., 2016; Goodwill & Kidgell, 2012; Hortobagyi et al., 2011; Kidgell et al., 2011, 2015; Leung et al., 2018; Mason et al., 2017; Urbin et al., 2015) or training status was not reported. 248 of 253 subjects were right-handed with an age of 18–35 years (but see (Urbin et al., 2015)).

Nine chronic studies trained an upper extremity muscle (Coombs et al., 2016; Hortobagyi et al., 2011; Kidgell et al., 2011, 2015; Leung et al., 2018; Manca et al., 2016; Mason et al., 2017; Urbin et al., 2015; Zult et al., 2016) and three targeted a leg muscle (Goodwill, Pearce, & Kidgell, 2012; Goodwill & Kidgell, 2012; Latella et al., 2012). Training duration lasted for three to eight weeks with nine to 24 sessions. All but two studies (Hortobagyi et al., 2011; Manca et al., 2016) used dynamic contractions. All studies used an intensity of 70%–100% of 1 RM, with a median of 80% of 1RM.

3.4. Primary outcomes

3.4.1. Acute studies

Measured at rest (Humphry et al., 2004; Triscott et al., 2008) or during a weak test contraction of the untrained muscle pair (Edgley & Winter 2004; Leung et al., 2015), ipsilateral CSE increased by 54.9% (± 16.4) (Humphry et al., 2004; Leung et al., 2015), decreased by 26–60.6% (Humphry et al., 2004; Triscott et al., 2008) or did not change (Edgley & Winter 2004; Leung et al., 2015) after an acute session of dynamic unilateral RT.

In acute studies using isometric training contractions, ipsilateral CSE, measured at rest (Baumer et al., 2002; Goodall et al., 2013; Hortobagyi et al., 2011; Schmidt et al., 2011; Takahashi et al., 2009) or during a weak test contraction of the trained (Gorsler et al., 2004) or untrained muscle pair (Lagerquist et al., 2012) remained unchanged or decreased by 15% five to 15 min after the intervention (Takahashi et al., 2009).

Ipsilateral SICI measured at rest (Baumer et al., 2002; Hortobagyi et al., 2011; Schmidt et al., 2011; Takahashi et al., 2009) or while contracting the untrained muscle pair (Leung et al., 2015) did not change or decreased by 39.2% (± 6.62) (Leung et al., 2015; Takahashi et al., 2009) after acute bouts of unilateral RT.

Ipsilateral ICF decreased by 27.3–96.7% (Baumer et al., 2002; Schmidt et al., 2011) immediately after training or did not change (Baumer et al., 2002; Hortobagyi et al., 2011; Takahashi et al., 2009).

Interhemispheric inhibition in the untrained muscle pair during low-intensity isometric contraction did not change (Edgley & Winter 2004), while it was acutely diminished (8.8 ± 3.9%) when measured at rest (Hortobagyi et al., 2011).

3.4.2. Chronic studies

Ipsilataeral CSE increased (Goodwill et al., 2012; Goodwill & Kidgell, 2012; Hortobagyi et al., 2011; Kidgell et al., 2011, 2015; Leung et al., 2018; Mason et al., 2017; Zult et al., 2016) or remained unchanged (Coombs et al., 2016; Latella et al., 2012; Leung et al., 2018; Manca et al., 2016; Urbin et al., 2015) after periods of chronic unilateral RT when measured at rest (Hortobagyi et al., 2011; Manca et al., 2016; Zult et al., 2016) or while the trained (Hortobagyi et al., 2011; Zult et al., 2016) or untrained muscle was weakly contracted (Coombs et al., 2016; Goodwill et al., 2012;

Goodwill & Kidgell, 2012; Kidgell et al., 2011, 2015; Latella et al., 2012; Leung et al., 2018; Manca et al., 2016; Mason et al., 2017; Urbin et al., 2015). After chronic unilateral RT, ipsilateral CSE increased by 27.7% (± 34.3). This mean change is based on data in nine studies that measured ipsilateral CSE at 20% of MSO above MT (Coombs et al., 2016; Goodwill et al., 2012; Kidgell et al., 2011; Latella et al., 2012) and 130% of AMT intensity (Leung et al., 2018; Mason et al., 2017) during low intensity contraction of the untrained muscle, and also on changes in ipsilateral CSE measured at 120% of the MT intensity during trained limb contraction (Zult et al., 2016) or at rest (Hortobagyi et al., 2011; Manca et al., 2016).

Ipsilateral SICI was measured at rest (Hortobagyi et al., 2011; Manca et al., 2016; Zult et al., 2016) and while subjects contracted the trained (Zult et al., 2016) or untrained muscle pair (Coombs et al., 2016; Goodwill et al., 2012; Goodwill & Kidgell, 2012; Kidgell et al., 2015; Leung et al., 2018). SICI in iM1 decreased by 32.9 ± 10.7% (Goodwill et al., 2012; Goodwill & Kidgell, 2012; Kidgell et al., 2015; Leung et al., 2018; Zult et al., 2016) or remained unchanged (Coombs et al., 2016; Hortobagyi et al., 2011; Kidgell et al., 2015; Leung et al., 2018; Manca et al., 2016; Zult et al., 2016) after chronic unilateral RT. Additionally, cSP was unchanged (Kidgell et al., 2011; Urbin et al., 2015) or became shorter by 21–26 m s (Latella et al., 2012; Mason et al., 2017), after chronic unilateral RT. cSP revealed large variation because it remained unchanged or shortened depending on contraction type (Kidgell et al., 2015), limb dominance (Coombs et al., 2016) or visual feedback (Zult et al., 2016) used in the chronic unilateral RT.

Interhemispheric inhibition measured at rest decreased (30.9 ± 3.8%) after 20 sessions of unilateral RT of the right FDI (Hortobagyi et al., 2011), increased (Zult et al., 2016) or remained unchanged after 12 sessions of unilateral RT (Manca et al., 2016). Chronic unilateral RT did not modify ICF (Hortobagyi et al., 2011; Manca et al., 2016).

The mean cross-education after chronic unilateral RT was 23.3 ± 14.4%. Fig. 2 shows that data from the same 9 studies used to calculate mean ipsilateral CSE changes correlated r = 0.649 (P < 0.01) with increases in maximal voluntary force of the untrained limb.

4. Discussion

Results from the present review show that chronic unilateral RT leads to increased ipsilateral CSE (n = 8 studies), and reduced ipsilateral SICI (n = 5 studies), cSP (n = 5 studies), and interhemispheric inhibition (n = 1 study). Such findings partially support the cross-activation model, by which the activation of the ipsilateral brain structures by the unilateral muscle contractions during unilateral RT, serves as the training stimulus for chronic adaptations in the ipsilateral brain areas. However, such cross-activation of iM1 does not to lead to similar response after an acute session of unilateral RT, in which the pattern of change in ipsilateral CSE (increased, n = 2 of 11), ipsilateral SICI (decreased, n = 2 of 5), or interhemispheric inhibition (did not change, n = 1) was much more variable.

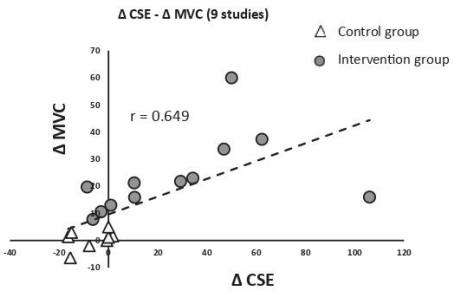

Fig. 2. Correlation between changes in ipsilateral corticospinal excitability and maximal voluntary force of the untrained limb.

The iM1 adaptations after chronic unilateral RT may reflect changes in the membrane properties of the corticospinal neurons, increases in the efficacy of the excitatory synapses, a decrease in the excitability of the GABAergic inhibitory interneurons, and/or reductions in the interhemispheric inhibition input from contralateral to ipsilateral cortex (Goodwill et al., 2012; Hortobagyi et al., 2011).

Such adaptations could be increasing the effectiveness of the motor command, thus contributing to cross-education after chronic unilateral RT. Fig. 2 shows that increases in ipsilateral CSE and cross-education correlate r = 0.649 (P < 0.01, n = 9 studies), suggesting that the change in ipsilateral CSE could be one of the mechanisms explaining the increase in maximal voluntary force in the untrained limb (Coombs et al., 2016; Goodwill et al., 2012; Hortobagyi et al., 2011; Kidgell et al., 2011; Latella et al., 2012; Leung et al., 2018; Manca et al., 2016; Mason et al., 2017; Zult et al., 2016). However we must be cautious with this interpretation because it is hampered by a lack of correlation reported in individual studies between changes in ipsilateral CSE and cross-education (Leung et al., 2018; Mason et al., 2017), and whether or not the level of ipsilateral CSE at baseline drives this relationship (Tallent, Goodall, Hortobagyi, St Clair Gibson, & Howatson, 2013). Indeed, a recent review reported zero association between skill learning and changes in CSE based on individual data (n = 251) from 11 studies (Berghuis, Semmler, Opie, Post, & Hortobagyi, 2017). In addition, results revealed high variability in iM1 excitability measured after a bout or a period of unilateral RT, with several chronic studies (n = 4 for ipsilateral CSE, n = 3 for SICI, n = 2 for cSP, and n = 2 for interhemispheric inhibition) reporting no changes in measures of iM1 excitability. However, the source of this variation may be related to differences in the training variables between studies such as the type of contraction, the intensity of training, the degree of fatigue or the external pacing of the movement, as discussed underneath.

4.1. Contraction type and intensity

Cross activation of iM1 is greater during dynamic eccentric than dynamic concentric or static unilateral voluntary muscle contractions, leading to higher ipsilateral CSE, and reduced ipsilateral SICI, and interhemispheric inhibition in the iM1 (Howatson et al., 2011; Uematsu et al., 2010). It is probably that this higher cross-activation is due to greater neural resources needed for programming and planning eccentric contractions in comparison to static or concentric contractions (Fang, Siemionow, Sahgal, Xiong, & Yue, 2001), or because of inhibitory and facilitatory influences from the dorsal premotor and posterior parietal cortices in the involved M1 and iM1 (Koch et al., 2007; Mochizuki, Huang, & Rothwell, 2004). Therefore, if unilateral eccentric muscle contractions lead to greater activation of the ipsilateral brain areas in comparison to static or pure concentric contractions, following the cross-activation model it is possible that eccentric or mixed (concentric and eccentric) contractions during unilateral RT could serve as a greater training stimulus for iM1 adaptations. In this regard, results from the acute studies show that those sessions that increased ipsilateral CSE and reduced SICI comprised dynamic contractions

(Humphry et al., 2004; Leung et al., 2015). Furthermore, the chronic studies reporting reductions in SICI and cSP (Coombs et al., 2016; Goodwill et al., 2012; Goodwill & Kidgell, 2012; Kidgell et al., 2015; Latella et al., 2012; Leung et al., 2018; Mason et al., 2017; Zult et al., 2016) used dynamic unilateral RT. For example, cross-education after chronic unilateral RT was greater after eccentric compared with concentric training and was accompanied by greater increases in ipsilateral CSE, and reductions in ipsilateral SICI and cSP duration (Kidgell et al., 2015). It thus seems that chronic unilateral RT comprising a movement element through eccentric or concentric muscle contractions compared with static efforts, contributes to increases in iM1 excitability.

Still, the results are not entirely consistent, as some acute (Edgley & Winter 2004) and chronic studies (Coombs et al., 2016; Kidgell et al., 2011, 2015; Latella et al., 2012; Urbin et al., 2015) found no effects of dynamic unilateral RT on measures of iM1 excitability. Furthermore, a recent meta-analysis observed no discernible effects of contraction type on chronic ipsilateral CSE and SICI adaptations (Manca, Hortobagyi, Rothwell, & Deriu, 2018). We thus tentatively suggest that the specific modulation of the iM1 during dynamic, in particular eccentric voluntary muscle contractions, due to higher neural resources needed and the differential activation of brain areas subserving the iM1 (Howatson et al., 2011), is likely to increase the iM1 excitability. However, factors other than contraction type may also contribute to changes in iM1 excitability after acute and chronic unilateral RT.

Training intensity can be one such training variable. Indeed strength gains seem to scale with contraction intensity used in resistance training (Schoenfeld, Grgic, Ogborn, & Krieger, 2017). Likewise, ipsilateral CSE parametrically increases (Muellbacher et al., 2000), and ipsilateral SICI and interhemispheric inhibition decrease during high intensity contractions (Perez & Cohen, 2008). Therefore, based on the cross-activation model, the higher ipsilateral brain activation because of the repeated high intensity contractions during unilateral RT, could serve as a greater training stimulus for iM1 adaptations in comparison with lower intensities. This prediction is compatible with the greater iM1 adaptations and cross-education occurring after chronic eccentric-based unilateral RT compared to concentric unilateral RT (Kidgell et al., 2015), because it is known that the torque performed during maximal eccentric contractions is 20–30% higher than during concentric actions (Griffin, Tooms, vander Zwaag, Bertorini, & O'Toole, 1993). However, a direct comparison of the effect of the intensity of chronic unilateral RT in iM1 adaptations with the included studies is not possible because all used high intensities between 70% and 100% of RM (dynamic studies) or MVC (static studies). Regarding acute studies, few showed an increase in ipsilateral CSE or a reduction in ipsilateral SICI without a clear relationship of those changes with the intensity used during training. Therefore, although high intensity muscle contractions evoke greater ipsilateral brain activation (Muellbacher et al., 2000), an experimental confirmation of the effect of this phenomenon in iM1 adaptations and cross-education is lacking.

4.2. Effect of fatigue

During prolonged submaximal contractions, motoneuron recruitment increase because of an increase in the excitatory drive to the motor units of the training muscle in compensation for reductions in muscular efficiency (Muddle et al., 2018). In addition, the amount of fatigue in the training limb is, together with the intensity, an important factor determining the presence and magnitude of associated EMG in the contralateral homologous muscle (Aranyi & Rosler, 2002). Because the associated EMG is probably a result of descending volleys generated by the cross-activation of iM1 (Zijdewind, Butler, Gandevia, & Taylor, 2006), it is likely that contractions leading to muscle failure (or near failure) would not only increase associated EMG but also iM1 activation. Therefore, according to the cross activation hypothesis (Lee & Carroll, 2007), the higher concurrent activation of iM1 with cM1 during fatiguing contractions could serve as a better training stimulus for increases in iM1 excitability and by extension for cross-education.

However, contrary to this hypothesis, (Humphry et al., 2004) observed a reduction of ipsilateral CSE when healthy volunteers performed an acute bout of dynamic unilateral RT to failure. Furthermore, they also found ipsilateral CSE facilitation when the set was performed until 25% of the volume needed to failure. In addition, other studies found that ipsilateral CSE decrease when subjects exercised to the point so that they were unable to perform the movement (Humphry et al., 2004; Triscott et al., 2008) or exert any force (Takahashi et al., 2009). With regards to other variables like ipsilateral SICI, interhemispheric inhibition, and ipsilateral ICF, no clear differences were found depending on the level of fatigue achieved during the training session (i.e.: leading or not to muscle failure). Furthermore, no studies have addressed yet the neuroplastic changes produced by chronic unilateral RT leading or not to muscle failure, which in terms of a regular weightlifting program is an essential variable (Pareja-Blanco et al., 2016). Therefore, more research is needed to determine the effects of fatigue in the training limb caused by acute and chronic unilateral RT on iM1 adaptations and cross-education.

4.3. Externally-vs. self-paced training

Practice of a simple or a skilled task with external compared with internal pacing of the movement leads to higher facilitation of corticospinal excitability of the trained side (Ackerley et al., 2007, 2011). The greater increase in CSE it is thought to be a consequence of the repeated arrival of afferent auditory inputs from the auditory cortex (through projections from the ipsilateral premotor and supplementary motor cortex to the M1) synchronized with the activation of corticospinal cells in the M1 during the muscle contractions, that lead to increased synaptic efficacy according to Hebbian principles (Jantzen, Steinberg, & Kelso, 2009). Furthermore, intracortical inhibition is decreased during synchronized contractions to an external auditory signal (Stinear & Byblow, 2003) and remains diminished after an acute or chronic period of externally paced unilateral RT in the trained limb (Leung et al., 2015, 2018).

Results from recent studies suggest that not only contralateral M1 but also iM1 plasticity is affected by the pacing strategy during unilateral RT, with externally paced movements leading to greater increases in iM1 excitability and reductions in SICI after both, acute and chronic unilateral RT (Leung et al., 2015, 2018). However, externally paced chronic unilateral RT also produced mixed results with respect to iM1 adaptations, as in some studies there were no changes in iM1 excitability or cSP decreased after chronic unilateral RT with the dominant limb but remained unchanged after non-dominant limb training despite the inclusion of externally paced unilateral RT (Coombs et al., 2016). Therefore, the data are mixed in support of greater increases in iM1 excitability after externally-vs. internally paced unilateral RT. Furthermore independent of its effect on iM1 adaptations, there is no evidence to suggest that cross-education is preferentially greater after externally-vs. internally-paced chronic unilateral RT. In fact, a recent study reported that externally-vs. internally-paced chronic unilateral RT, did result in higher iM1 adaptations, however such changes were not coupled with greater strength increases in the trained and the untrained limb when compared to internally-paced training (Leung et al.,

2018).

5. Conclusions

In conclusion, results from the present review show a high heterogeneity in the response of iM1 to an acute bout, but also after a chronic period of unilateral RT. It can not be ruled out that the contradictory effects on iM1 could be a consequence of the methodology approach. For example, as described in the results section, one of the main variations in the measurement of ipsilateral CSE and SICI is the situation in which they were measured (during contraction or at rest). It is likely that in order to detect possible neurophysiological adaptations after a training period, the task in which measures are performed, should be similar, if not equal, to the task done during training (Beck et al., 2007). Furthermore, a more homogeneous methodology of measurements could facilitate the comparison of results between studies, thus helping to determine the differential effect of training variables like those discussed in this review on the iM1 measurements and its relation to cross-education.

However, apart from the methodology approach, the high heterogeneity in the response of the iM1 to acute and chronic unilateral RT seems to be related to the training configuration itself, which could trigger different iM1 adaptations. In this regard, the tentative conclusion is that high intensity, eccentric or externally paced muscle contractions are the more effective training variables to increase iM1 excitability. Notwithstanding, cross-education can occur in the absence of such changes whereby, the mechanism of cross-education examined with TMS remains unclear. Maybe structures other than iM1 that TMS cannot probe and that are bilaterally activated during unilateral contractions, like supplementary motor area, sensory regions, prefrontal, premotor, cingulate and parietal cortices, or cerebellum (Dai et al., 2001), could also be related to cross-education (Farthing, Borowsky, Chilibeck, Binsted, & Sarty, 2007; Ruddy & Carson, 2013). However, further research should shed more light on the effects of intensity (i.e.: comparing low-load to heavy-load unilateral RT) and fatigue (i.e.: comparing unilateral RT using sets leading or not to muscle failure) on cross-education and its underlying neural mechanism. This is important in order to maximize the benefits of the unilateral RT as a tool to reduce asymmetries in different athletic samples, as well as in patients with orthopaedic or neurological impairments.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ptsp.2019.09.006.

Conflicts of interest

None declared.

Ethical approval

Ethical approval was not required.

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References

Ackerley, S. J., Stinear, C. M., & Byblow, W. D. (2007). The effect of coordination mode on use-dependent plasticity. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 118*(8), 1759–1766.

Ackerley, S. J., Stinear, C. M., & Byblow, W. D. (2011). Promoting use-dependent plasticity with externally-paced training. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 122*(12), 2462–2468.

Aranyi, Z., & Rosler, K. M. (2002). Effort-induced mirror movements. A study of transcallosal inhibition in humans. *Experimental Brain Research, 145*(1), 76–82.

Baumer, T., Munchau, A., Weiller, C., & Lieper, J. (2002). Fatigue suppresses ipsilateral intracortical facilitation. *Experimental Brain Research, 146*(4), 467–473.

Beck, S., Taube, W., Gruber, M., Amtage, F., Gollhofer, A., & Schubert, M. (2007). Task-specific changes in motor evoked potentials of lower limb muscles after different training interventions. *Brain Research, 1179*, 51–60.

Berghuis, K. M. M., Semmler, J. G., Opie, G. M., Post, A. K., & Hortobagyi, T. (2017). Age-related changes in corticospinal excitability and intracortical inhibition after upper extremity motor learning: A systematic review and meta-analysis. *Neurobiology of Aging, 55*, 61–71.

Coombs, T. A., Frazer, A. K., Horvath, D. M., Pearce, A. J., Howatson, G., & Kidgell, D. J. (2016). Cross-education of wrist extensor strength is not influenced by non-dominant training in right-handers. *European Journal of Applied Physiology, 116*(9), 1757–1769.

Dai, T. H., Liu, J. Z., Sahgal, V., Brown, R. W., & Yue, G. H. (2001). Relationship between muscle output and functional MRI-measured brain activation. *Experimental Brain Research, 140*(3), 290–300.

Edgley, S. A., & Winter, A. P. (2004). Different effects of fatiguing exercise on corticospinal and transcallosal excitability in human hand area motor cortex. *Experimental Brain Research, 159*(4), 530–536.

Fang, Y., Siemionow, V., Sahgal, V., Xiong, F., & Yue, G. H. (2001). Greater movement-related cortical potential during human eccentric versus concentric muscle contractions. *Journal of Neurophysiology, 86*(4), 1764–1772.

Farthing, J. P., Borowsky, R., Chilibeck, P. D., Binsted, G., & Sarty, G. E. (2007). Neurophysiological adaptations associated with cross-education of strength. *Brain Topography, 20*(2), 77–88.

Goodall, S., Gibson, A. S., Voller, B., Lomarev, M., Howatson, G., Dang, N., et al. (2013). Repetitive transcranial magnetic stimulation attenuates the perception of force output production in non-exercised hand muscles after unilateral exercise. *PLoS One, 8*(11), 9.

Goodwill, A. M., & Kidgell, D. J. (2012). The effects of whole-body vibration on the cross-transfer of strength. *TheScientificWorldJOURNAL, 2012*, 504837.

Goodwill, A. M., Pearce, A. J., & Kidgell, D. J. (2012). Corticomotor plasticity following unilateral strength training. *Muscle & Nerve, 46*(3), 384–393.

Gorsler, A., Zittel, S., Weiller, C., Munchau, A., & Liepert, J. (2004). Modulation of motor cortex excitability induced by pinch grip repetition. *Journal of Neural Transmission, 111*(8), 1005–1016 (Vienna, Austria: 1996).

Griffin, J. W., Tooms, R. E., vander Zwaag, R., Bertorini, T. E., & O'Toole, M. L. (1993). Eccentric muscle performance of elbow and knee muscle groups in untrained men and women. *Medicine & Science in Sports & Exercise, 25*(8), 936–944.

Harris, J. D., Quatman, C. E., Manring, M. M., Siston, R. A., & Flanigan, D. C. (2014). How to write a systematic review. *The American Journal of Sports Medicine, 42*(11), 2761–2768.

Hortobagyi, T., Richardson, S. P., Lomarev, M., Shamim, E., Meunier, S., Russman, H., et al. (2011). Interhemispheric plasticity in humans. *Medicine & Science in Sports & Exercise, 43*(7), 1188–1199.

Howatson, G., Taylor, M. B., Rider, P., Motawar, B. R., McNally, M. P., Solnik, S., et al. (2011). Ipsilateral motor cortical responses to TMS during lengthening and shortening of the contralateral wrist flexors. *European Journal of Neuroscience, 33*(5), 978–990.

Humphry, A. T., Lloyd-Davies, E. J., Teare, R. J., Williams, K. E., Strutton, P. H., & Davey, N. J. (2004). Specificity and functional impact of post-exercise depression of cortically evoked motor potentials in man. *European Journal of Applied Physiology, 92*(1–2), 211–218.

Jantzen, K. J., Steinberg, F. L., & Kelso, J. A. (2009). Coordination dynamics of large-scale neural circuitry underlying rhythmic sensorimotor behavior. *Journal of Cognitive Neuroscience, 21*(12), 2420–2433.

Kidgell, D. J., Frazer, A. K., Daly, R. M., Rantalainen, T., Ruotsalainen, I., Ahtiainen, J., et al. (2015). Increased cross-education of muscle strength and reduced corticospinal inhibition following eccentric strength training. *Neuroscience, 300*, 566–575.

Kidgell, D. J., Stokes, M. A., & Pearce, A. J. (2011). Strength training of one limb increases corticomotor excitability projecting to the contralateral homologous limb. *Motor Control, 15*(2), 247–266.

Koch, G., Fernandez Del Olmo, M., Cheeran, B., Ruge, D., Schippling, S., Caltagirone, C., et al. (2007). Focal stimulation of the posterior parietal cortex increases the excitability of the ipsilateral motor cortex. *Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 27*(25), 6815–6822.

Kristeva, R., Cheyne, D., & Deecke, L. (1991). Neuromagnetic fields accompanying unilateral and bilateral voluntary movements: Topography and analysis of cortical sources. *Electroencephalography and Clinical Neurophysiology, 81*(4), 284–298.

Lagerquist, O., Mang, C. S., & Collins, D. F. (2012). Changes in spinal but not cortical excitability following combined electrical stimulation of the tibial nerve and voluntary plantar-flexion. *Experimental Brain Research, 222*(1–2), 41–53.

Latella, C., Kidgell, D. J., & Pearce, A. J. (2012). Reduction in corticospinal inhibition in the trained and untrained limb following unilateral leg strength training. *European Journal of Applied Physiology, 112*(8), 3097–3107.

Lee, M., & Carroll, T. J. (2007). Cross education: Possible mechanisms for the

contralateral effects of unilateral resistance training. *Sports Medicine (Auckland, NZ), 37*(1), 1–14.
Leung, M., Rantalainen, T., Teo, W. P., & Kidgell, D. (2015). Motor cortex excitability is not differentially modulated following skill and strength training. *Neuroscience, 305*, 99–108.
Leung, M., Rantalainen, T., Teo, W. P., & Kidgell, D. (2018). The ipsilateral cortico-spinal responses to cross-education are dependent upon the motor-training intervention. *Experimental Brain Research, 9*(1857).
Maher, C. G., Sherrington, C., Herbert, R. D., Moseley, A. M., & Elkins, M. (2003). Reliability of the PEDro scale for rating quality of randomized controlled trials. *Physical Therapy, 83*(8), 713–721.
Manca, A., Ginatempo, F., Cabboi, M. P., Mercante, B., Ortu, E., Dragone, D., et al. (2016). No evidence of neural adaptations following chronic unilateral isometric training of the intrinsic muscles of the hand: A randomized controlled study. *European Journal of Applied Physiology, 116*(10), 1993–2005.
Manca, A., Hortobagyi, T., Rothwell, J. C., & Deriu, F. (2018). Neurophysiological adaptations in the untrained side in conjunction with cross-education of muscle strength: A systematic review and meta-analysis. *Journal of Applied Physiology, 124*(6) (Bethesda, Md: 1985).
Mason, J., Frazer, A. K., Horvath, D. M., Pearce, A. J., Avela, J., Howatson, G., et al. (2017). Ipsilateral corticomotor responses are confined to the homologous muscle following cross-education of muscular strength. *Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme, 43*(1).
Mochizuki, H., Huang, Y. Z., & Rothwell, J. C. (2004). Interhemispheric interaction between human dorsal premotor and contralateral primary motor cortex. *The Journal of Physiology, 561*(Pt 1), 331–338.
Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., et al. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews, 4*, 1.
Muddle, T. W. D., Colquhoun, R. J., Magrini, M. A., Luera, M. J., DeFreitas, J. M., & Jenkins, N. D. M. (2018). Effects of fatiguing, submaximal high- versus low-torque isometric exercise on motor unit recruitment and firing behavior. *Physics Reports, 6*(8), e13675.
Muellbacher, W., Facchini, S., Boroojerdi, B., & Hallett, M. (2000). Changes in motor cortex excitability during ipsilateral hand muscle activation in humans. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 111*(2), 344–349.
Munn, J., Herbert, R. D., & Gandevia, S. C. (2004). Contralateral effects of unilateral resistance training: A meta-analysis. *Journal of Applied Physiology, 96*(5), 1861–1866 (Bethesda, Md: 1985).
Narici, M. V., Roi, G. S., Landoni, L., Minetti, A. E., & Cerretelli, P. (1989). Changes in force, cross-sectional area and neural activation during strength training and detraining of the human quadriceps. *European Journal of Applied Physiology and Occupational Physiology, 59*(4), 310–319.
National Heart LaBI, National Institutes of Health. (2014). *Quality assessment tool for before-after (Pre-post) studies with No control group*.
Pareja-Blanco, F., Rodriguez-Rosell, D., Sanchez-Medina, L., Ribas-Serna, J., Lopez-Lopez, C., Mora-Custodio, R., et al. (2016). Acute and delayed response to resistance exercise leading or not leading to muscle failure. *Clinical Physiology and Functional Imaging, 37*(6).
Perez, M. A., & Cohen, L. G. (2008). Mechanisms underlying functional changes in the primary motor cortex ipsilateral to an active hand. *Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 28*(22), 5631–5640.
Perez, M. A., & Cohen, L. G. (2009). Scaling of motor cortical excitability during unimanual force generation. *Cortex, 45*(9), 1065–1071.
Perez, M. A., Tanaka, S., Wise, S. P., Sadato, N., Tanabe, H. C., Willingham, D. T., et al. (2007). Neural substrates of intermanual transfer of a newly acquired motor skill. *Current Biology, 17*(21), 1896–1902.
Ruddy, K. L., & Carson, R. G. (2013). Neural pathways mediating cross education of motor function. *Frontiers in Human Neuroscience, 7*, 397.
Schmidt, M. W., Hinder, M. R., Summers, J. J., & Garry, M. I. (2011). Long-lasting contralateral motor cortex excitability is increased by unilateral hand movement that triggers electrical stimulation of opposite homologous muscles. *Neurorehabilitation and Neural Repair, 25*(6), 521–530.
Schoenfeld, B. J., Grgic, J., Ogborn, D., & Krieger, J. W. (2017). Strength and hypertrophy adaptations between low- versus high-load resistance training: A systematic review and meta-analysis. *The Journal of Strength & Conditioning Research/National Strength & Conditioning Association, 31*(12).
Schulze, K., Luders, E., & Jancke, L. (2002). Intermanual transfer in a simple motor task. *Cortex, 38*(5), 805–815.
Stinear, C. M., & Byblow, W. D. (2003). Role of intracortical inhibition in selective hand muscle activation. *Journal of Neurophysiology, 89*(4), 2014–2020.
Takahashi, K., Maruyama, A., Maeda, M., Etoh, S., Hirakoba, K., Kawahira, K., et al. (2009). Unilateral grip fatigue reduces short interval intracortical inhibition in ipsilateral primary motor cortex. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 120*(1), 198–203.
Tallent, J., Goodall, S., Hortobagyi, T., St Clair Gibson, A., & Howatson, G. (2013). Corticospinal responses of resistance-trained and un-trained males during dynamic muscle contractions. *Journal of Electromyography and Kinesiology: Official Journal of the International Society of Electrophysiological Kinesiology, 23*(5), 1075–1081.
Triscott, S., Gordon, J., Kuppuswamy, A., King, N., Davey, N., & Ellaway, P. (2008). Differential effects of endurance and resistance training on central fatigue. *Journal of Sports Sciences, 26*(9), 941–951.
Uematsu, A., Obata, H., Endoh, T., Kitamura, T., Hortobagyi, T., Nakazawa, K., et al. (2010). Asymmetrical modulation of corticospinal excitability in the contracting and resting contralateral wrist flexors during unilateral shortening, lengthening and isometric contractions. *Experimental Brain Research, 206*(1), 59–69.
Urbin, M. A., Harris-Love, M. L., Carter, A. R., & Lang, C. E. (2015). 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. *Frontiers in Neurology, 6*, 119.
Zijdewind, I., Butler, J. E., Gandevia, S. C., & Taylor, J. L. (2006). The origin of activity in the biceps brachii muscle during voluntary contractions of the contralateral elbow flexor muscles. *Experimental Brain Research, 175*(3), 526–535.
Zult, T., Goodall, S., Thomas, K., Solnik, S., Hortobagyi, T., & Howatson, G. (2016). Mirror training augments the cross-education of strength and affects inhibitory paths. *Medicine & Science in Sports & Exercise, 48*(6), 1001–1013.

ANNEX 5: Study 3. Reference: Colomer-Poveda D, Hortobagyi T, Keller M, Romero-Arenas S, Marquez G. Training intensity-dependent increases in corticospinal but not intracortical excitability after acute strength training. Scandinavian journal of medicine & science in sports. 2020;30(4):652-61. doi: 10.1111/sms.13608

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ORIGINAL ARTICLE

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Training intensity-dependent increases in corticospinal but not intracortical excitability after acute strength training

David Colomer-Poveda[1] | **Tibor Hortobágyi**[2] | **Martin Keller**[3] | **Salvador Romero-Arenas**[1] | **Gonzalo Márquez**[1]

[1]Department of Physical Education and Sport, Faculty of Sport, Catholic University of Murcia (UCAM), Murcia, Spain

[2]Center for Human Movement Sciences, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[3]Department of Sport, Exercise and Health, University of Basel, Basel, Switzerland

Correspondence
David Colomer-Poveda, Facultad de Deporte - Universidad Católica de Murcia, Campus de los Jerónimos s/n, Guadalupe, 30107 Murcia, Spain.
Email: dcolomer@ucam.edu

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The purpose of this study was to determine whether the increases in corticospinal excitability (CSE) observed after one session of unilateral isometric strength training (ST) are related to changes in intracortical excitability measured by magnetic brain stimulation (TMS) in the trained and the contralateral untrained biceps brachii (BB) and whether such changes scale with training intensity. On three separate days, 15 healthy young men performed one ST session of 12 sets of eight isometric contractions of the right elbow flexors at 0% (control session), 25%, or 75% of the maximal voluntary contraction (MVC) in a random order. Before and after each session separated at least by 1 week, motor evoked potential (MEP) amplitude, short-interval intracortical inhibition (SICI), contralateral silent period (SP), and intracortical facilitation (ICF) generated by TMS were measured in the trained and the untrained BBs. Compared with baseline, MEPs recorded from the trained BB increased by ~47% after training at 75% of MVC ($P < .05$) but not after training at 0% (~4%) or 25% MVC (~5%, both $P > .05$). MEPs in the untrained BB and SICI, SP, and ICF in either BB did not change. Therefore, acute high-intensity but not low-intensity unilateral isometric ST increases CSE in the trained BB without modifications in intracortical inhibition or facilitation. Thus, increases in corticospinal neurons or α-α-motoneuron excitability could underlie the increases in CSE. Regardless of contraction intensity, acute isometric ST did not modify the excitability of the ipsilateral primary motor cortex measured by TMS.

KEYWORDS
cross-education, intracortical facilitation, ipsilateral M1, short-interval intracortical inhibition, silent period, strength training

1 | INTRODUCTION

Strength training (ST) is an effective means to increase maximal voluntary (MVC) force and muscle mass.[1-3] The chronic increases in MVC force after ST are usually accompanied by neural adaptations at a supraspinal[1,2] and spinal level.[3] However, little is known about how fast such neural adaptations occur after beginning a ST program. Recent studies have shown that even just a single ST session can evoke spinal and cortical modulations[4-6] as determined by electrical stimulation at the mastoid process and transcranial magnetic stimulation (TMS) over the contralateral primary motor cortex (cM1), respectively. Indeed, acute ST increased the synaptic efficacy of neural transmission in the corticospinal tract, α-motoneuron excitability, and/or cM1 excitability.[5,6] Furthermore, there are indications for contraction intensity-dependent effects of ST on corticospinal excitability (CSE) measured by TMS because high vs low training

loads produced more pronounced and longer-lasting changes in neuronal excitability.[6] However, changes in spinal excitability measured by cervicomedullary electrical stimulation did not produce such intensity-dependent effects.[6] This suggests that cM1 is more sensitive to the intensity of muscle contraction used in acute ST compared with α-motoneurons, supporting the hypothesis that short-term neural adaptations to ST occur at the supraspinal level.

A dose-response relationship in the responses to corticospinal but not spinal stimulation following acute ST could reflect the involvement of cM1 circuits.[7] Intracortical circuits can inhibit or facilitate the responses to TMS in cM1.[8] Gamma aminobutyric acid (GABA) is the main inhibitory neurotransmitter in cM1, which acts mainly through interneurons with GABAa receptors, responsible for fast synaptic inhibition, and GABAb receptors, responsible for slower but longer-lasting inhibition.[9] Both forms of inhibition can be measured with paired- and single-pulse TMS, respectively.[10,11] Although both forms of inhibition are mediated by different populations of interneurons, these project to higher-threshold circuits that activate the corticospinal tract neurons, ultimately reducing cM1 excitability.[8] Therefore, although there is still no evidence of a relationship between chronic changes in intracortical inhibition and the force of a muscle contraction, decreases in the efficacy of those inhibitory intracortical circuits can release cM1 from inhibition, increasing cM1 excitability, the efficacy of the motor command, and the drive to muscles to contract more forcefully. In fact, chronic ST tends to decrease short-interval intracortical inhibition (SICI) and silent period (SP) duration,[2,12] suggesting that a release of intracortical inhibition could be one mechanism underlying the chronic increases in cM1 excitability and in the effectiveness of the motor command to increase MVC force. However, the time course of such adaptations is unclear because results from acute studies are inconsistent.[7,13-15] In addition to reductions in SICI or SP, an increase in intracortical facilitation (ICF) could also contribute to the increase in CSE. ICF is thought to involve corticocortical pyramidal cells with glutaminergic synapses projecting to the cortical neurons that activate the corticospinal tract.[16] However, little is known about changes in ICF after an acute session of ST, with two studies showing little or no changes.[13,15]

Therefore, because spinal mechanisms cannot fully account for the changes in CSE in relation to the ST intensity,[6] changes in intracortical circuits could be the main mechanisms modulating CSE. Indeed, contrary to what happens with CSE, which increases with contraction intensity (up to a limit), SICI tends to decrease with the intensity of the voluntary drive.[17] We could thus expect that high-intensity compared with low-intensity ST would have a greater potential to modify intracortical circuits, accounting for the greater responses to TMS after a single session of high- vs low-intensity ST.[6]

A unilateral voluntary muscle contraction can also activate ipsilateral brain areas.[18,19] Such cross-activation could be the source of adaptations in the untrained hemisphere, underlying increases in MVC force in the untrained homologous muscle when unilateral muscle contractions are repeated for a period of at least 3 weeks.[1,20,21] However, it is unknown whether, akin to the trained side,[4-6] neural modulations in the untrained hemisphere are already present after just one session of ST, or whether more training sessions are needed for neural changes to occur. Furthermore, because the excitability of the M1 ipsilateral to the contracting muscle (iM1) increases during discrete unimanual muscle contractions in an intensity-dependent manner,[19,22] we hypothesize that acute ST would also induce intensity-dependent changes in iM1 excitability.

Therefore, the purpose of the present study was to determine whether the increase in CSE after one session of ST is related to changes in SICI, SP, and ICF and whether such changes would occur in an intensity-dependent manner in the trained and the untrained biceps brachii (BB). A detailed understanding of the time course of adaption to ST and its dependency on contraction intensity has important implications for patients with neuromuscular conditions and older adults who might be unable to participate in high-intensity ST protocols.

2 | MATERIAL AND METHODS

2.1 | Participants

Healthy, right-handed, and recreationally active men (2-3 hours per week of recreational sports activities or aerobic training, age, 23.93 ± 4.65 years, n = 15) with no reported contraindications to TMS and not currently taking any medications volunteered to participate in the study. One week before the start of the experiments, participants were familiarized with peripheral nerve stimulation, TMS, and MVC protocols. Participants were asked to refrain from consuming alcoholic or caffeinated beverages and from exercising for at least 24 hours before each experimental session. The Institutional Review Board of the Catholic University of Murcia approved the protocol. Written informed consent was obtained from all participants before the start of the study. The experiments were performed in accordance with the latest version of the declaration of Helsinki.

2.2 | Experimental procedures

Each subject completed in a random order each of the three ST sessions at 0% (control [CON]), 25%, and 75% of MVC, one intensity per session, with each session separated by 1 week. The CON session consisted of 20 minutes of rest in

the posture used in training. ST sessions consisted of 12 sets of eight isometric right elbow flexor contractions ramped to 25% or 75% of MVC over 2 seconds. After reaching the target force, participants relaxed the elbow flexors and rested for 4 seconds. There was 1 minute of rest between sets.

Before (PRE) and after (POST) each intervention, one block of measurements with TMS (single- and paired-pulse) and brachial plexus stimulation was obtained from both arms during a low-level contraction of 5% of MVC. POST measurements started always in the left arm around 30 seconds after the last training set. Each block of measurement consisted of eight maximal compound muscle action potentials (M_{max}), 20 single-pulse motor evoked potentials (MEPs), and 40 paired-pulse stimulations (20 for SICI and 20 for ICF). All stimuli were separated by 5, and 30 seconds of rest was given after 15 pulses to avoid fatigue, so each block lasted for ~7 minutes. Additionally, five single-pulse MEPs at 120% of active motor threshold ($MEP_{25\%}/M_{max}$) and its respective SP were obtained in both BBs during 3-second-long contractions at 25% of MVC immediately before training or control period and at POST (approximately 10-15 minutes after training or control period ended; see Figure 1). Single-pulse stimulation during 25% vs 5% of MVC contractions allowed us to obtain clearer silent periods.

Before measurements, participants performed three MVCs with each arm separately. MVCs lasted for 3 seconds with 120 seconds of rest between trials. The posture during MVC tests and main measurements was identical. All trials were measured with two force transducers (NeuroLog System, Digitimer) firmly attached to the left or right wrist with a rigid strap. The highest MVC in each arm was used to determine the subsequent target force during measurements (5% and 25% of MVC) and training (25% or 75% of MVC).

2.3 | Setup

During testing, participants sat in a chair in front of a table with both shoulders flexed at 90° and the elbows flexed with forearms supinated and vertical (Figure 1). In this position, both forearms were fastened with a rigid strap to a force transducer (NL63-200 Kg; Digitimer) to measure voluntary force, which was displayed on a computer monitor in front of the participants.

Surface electromyography (EMG) was recorded from the right and left BB with Ag-AgCl surface electrodes in a belly-tendon montage (5-8 cm interelectrode distance). EMG was amplified (×200 or ×300 depending on the M_{max} amplitude), band-pass–filtered (10-1000 Hz), and sampled (2 kHz) with a Digitimer d440 isolated amplifier (Digitimer). Force recordings were band-pass–filtered (5-2500 Hz), amplified (×2500), and sampled at 2 kHz using a NeuroLog System (Digitimer). Both EMG and force recordings were simultaneously collected using an analog-digital board CED Micro1401-3 (Cambridge Electronic Design) for further analysis.

2.4 | Brachial plexus stimulation

For recording the M_{max} in each BB, single-pulse stimulation (200 μs duration) was delivered to the brachial plexus with a DS7AH constant current electrical stimulator (Digitimer). The cathode (pre-gelled Ag-AgCl electrodes) was positioned in the supraclavicular fossa and the anode on the acromion. After defining the stimulation intensity needed to evoke the M_{max} in each BB, the intensity was set to 120% of this value for the measurements (range: 42-186 mA).

2.5 | Transcranial magnetic stimulation

Single- and paired-pulse TMS was delivered to left (cM1) and right (iM1) motor cortices with a figure of eight coils (70 mm diameter) connected to two DuoMAG (Rogue Resolutions Ltd.) magnetic stimulators. The coil was oriented with the handle at ~45° posterolaterally to the midline, and the optimal stimulation location in each M1 was obtained by exploring the estimated center of the BB motor cortical representation. The point where stimulation produced the largest MEP in the contralateral BB was marked directly on the scalp with a permanent marker. Active motor threshold (AMT) was defined as the lowest stimulation intensity needed to obtain three out of five MEPs of a peak-to-peak amplitude >200 μV during a 5% MVC force, displayed as target on the monitor in front of the participant. To measure SICI and ICF, a paired-pulse protocol was used in which the conditioning pulse (CS) and the test pulse (TS) set at 80% and 120% of the AMT, respectively. The interstimulus interval was set to 3 ms (SICI) and 10 ms (ICF).

2.6 | Data analysis

The peak-to-peak amplitudes of M_{max} and MEPs were measured. MEP amplitudes were normalized to M_{max} within each measurement block and averaged ($MEP_{5\%}/M_{max}$ and $MEP_{25\%}/M_{max}$). Pre-stimulus rmsEMG activity was determined in a 150-ms window prior to each electrical or magnetic stimulus. Trials with rmsEMG larger or lower than the mean of each measurement block ±2 SDs were removed from the analysis. The SP duration was quantified as the time between the stimulus and the time at which the post-stimulus EMG returned to the 50% of the mean of the pre-stimulus (150-ms time window) background EMG activity.[23]

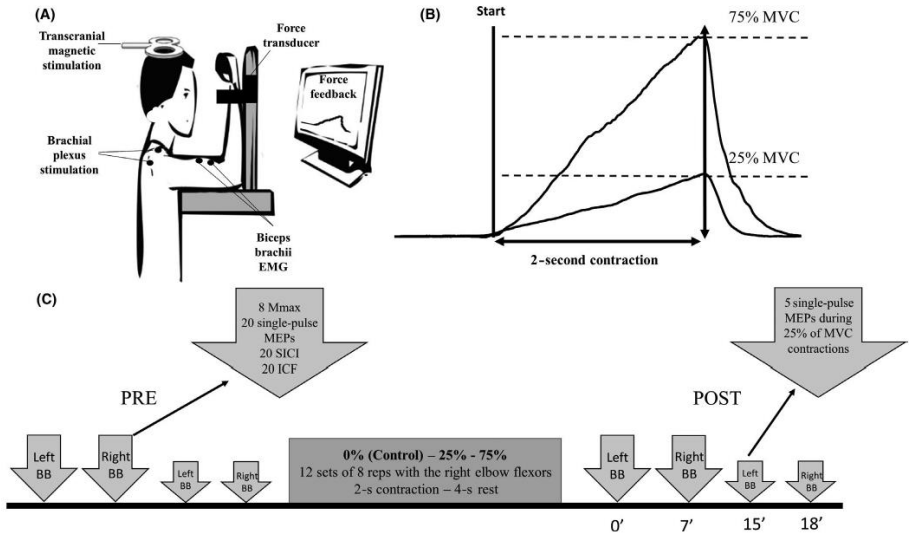

FIGURE 1 Schematic view of the setup and protocol. A, Participants completed the experiment seated with the elbow and the shoulder flexed to 90°. Visual feedback of the force was provided on a screen in front of the participants. B, Raw traces of a contraction from each training session from a representative subject. In each training session, the participants steadily contracted their BB until the required intensity marked with a horizontal line during a 2-s period identified with 2 vertical bars. C, Motor evoked potentials were obtained before (PRE) and after (POST) each session (CON, 25%, or 75% of MVC)

2.7 | Statistics

All data were first screened for normality using a Kolmogorov-Smirnov test. Intersession reliability of baseline M_{max}, single-, and paired-pulse TMS responses across sessions was determined using intraclass correlation coefficients (ICC (2, 1) two-way mixed effect model) with 95% confidence intervals (95% CIs). The ICC was interpreted with values below 0.5 indicating low reliability, values between 0.5 and 0.75 indicating moderate reliability, values between 0.75 and 0.9 indicating good reliability, and values higher than 0.90 indicating excellent reliability.[24] Then, a two-way repeated measures analysis of variance (RM-ANOVA) was performed with TIME (PRE and POST) and INTENSITY (CON, 25%, and 75%) as factors for pre-stimulus rmsEMG, M_{max}, $MEP_{5\%}/M_{max}$, $MEP_{25\%}/M_{max}$, SP, SICI, and ICF. Limb was not included as a factor in the ANOVA because post-measurements in the trained and the untrained were not simultaneous (immediately after vs ~7 minutes after, respectively). If sphericity was violated (Mauchly's test), degrees of freedom were corrected by Greenhouse-Geisser estimates of sphericity. When a nonsignificant main effect or interaction had a medium ES ($\eta_p^2 > 0.13$), paired comparisons and Cohen's *d* effect sizes were also computed. Effect sizes are presented as partial eta-square values (η_p^2; small: 0.02; medium: 0.13; large: 0.26). Unless indicated otherwise, data are reported as mean ± standard deviation. 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 for M_{max}, $MEP_{5\%}/M_{max}$, SICI (%TS), ICF (%TS), SP, and $MEP_{25\%}/M_{max}$ was good to excellent (ICC = 0.79-0.94, Table 1) in the trained and the untrained BB.

3.2 | Trained side

One subject was excluded from the statistical analysis only for the SICI variable because a consistent facilitation of more than 40% in both BBs. Pre-stimulus rmsEMG remained constant during all training sessions (See Table 2 in supporting information). $MEP_{5\%}/M_{max}$ amplitudes increased by +46.7%

TABLE 1 PRE measurements intersession reliability of M_{max}, $MEP_{5\%}/M_{max}$, SICI, ICF, SP, and $MEP_{25\%}/M_{max}$

	Trained intersession ICC (95% CI)	Untrained intersession ICC (95% CI)
M_{max}	0.90 (0.77, 0.96)	0.83 (0.60, 0.94)
$MEP_{5\%}/M_{max}$	0.80 (0.52, 0.90)	0.82 (0.56, 0.93)
SICI (%TS)	0.82 (0.58, 0.93)	0.94 (0.85, 0.98)
ICF (%TS)	0.86 (0.66, 0.95)	0.85 (0.64, 0.94)
SP	0.79 (0.52, 0.92)	0.89 (0.73, 0.96)
$MEP_{25\%}/M_{max}$	0.91 (0.78, 0.97)	0.92 (0.82, 0.97)

Abbreviations: CI, confident interval; ICC, intraclass correlation coefficient; ICF, intracortical facilitation; MEP, motor evoked potential; M_{max}, maximal compound muscle action potential; SICI, short-interval intracortical inhibition; SP, silent period.

($P = .04$, ES = 0.43, 95% CI = 0.31, 0.58) only after ST at 75% MVC but not after ST at 25% MVC (+4.8%, $P = .44$, ES = 0.08, 95% CI = −0.18, 0.25) or CON (+4.4%, $P = .76$, ES = 0.04, 95% CI = −0.38, 0.36; Figure 2). Baseline (PRE) $MEP_{5\%}/M_{max}$ amplitudes were equal between sessions (CON vs 25% $P = .46$, CON vs 75% $P = .99$, 25% vs 75% $P = .19$); however, training at 75% of MVC produced higher post-training $MEP_{5\%}/M_{max}$ amplitudes than the CON session ($P = .04$, ES = 0.32, 95% CI = −0.01, 0.77) and revealed a trend toward significance compared with 25% session ($P = .06$, ES = 0.54, 95% CI = 0.29, 0.87).

A single session of ST at 0%, 25%, and 75% MVC did not affect $MEP_{25\%}/M_{max}$, SP, ICF, and M_{max} (Table 2 in supporting information). However, although RM-ANOVA did not show significant effects or interactions for SICI, there was a medium effect size for the Time*Session interaction ($P = .09$, $\eta_p^2 = 0.17$) that revealed a small increase in SICI after the 75% of MVC ST session (from 76.8% to 69.1% of TS, $P = .01$, ES = −0.26, 95.0% CI = −0.41, −0.13).

3.3 | Untrained side

Pre-stimulus rmsEMG remained constant during all training sessions (See Table 3 in supporting information). A single session of ST at 0%, 25%, or 75% MVC did not modify $MEP_{5\%}/M_{max}$, $MEP_{25\%}/M_{max}$, SP, SICI, ICF, and M_{max} in the untrained BB (Table 3 in supporting information).

4 | DISCUSSION

We determined the effects of acute unilateral isometric ST of the right elbow flexors at 0%, 25%, and 75% MVC on CSE, SICI, ICF, and SP in the trained and untrained arms. Only acute ST training at 75% MVC did increase CSE in the trained BB measured during a 5% background MVC. Contrary to the hypothesis, the increases in CSE were not accompanied by a decline in intracortical inhibition or an increase in intracortical facilitation. The effects of a single session of ST at 0%, 25%, and 75% MVC were limb-specific, as no changes occurred in any of the TMS measures obtained in iM1.

4.1 | Trained side

A single session of ST increases the responses to corticospinal tract stimulation at rest[4-6] or during low-level isometric contractions[7,15] suggesting increases in cortical or α-motoneuron excitability or an increased efficacy of the corticospinal-motorneuronal synapse.[5,6] Our results are in line with previous studies by showing ~47% increase in CSE measured at 5% background MVC in the BB of the trained arm only after ST at 75% MVC. The present data confirm the previously described effect of intensity[6] by showing a 75%—MVC intensity—threshold of acute ST to produce meaningful changes in CSE, suggesting that training intensity is a determinant of acute corticospinal plasticity in response to a bout of isometric ST.

Although the coil of TMS is placed over the cM1, the response to single-pulse TMS is not only affected by cortical neuron excitability. Single-pulse TMS reflects the excitability of corticospinal neurons and interneurons projecting onto these neurons in M1 as well as the excitability of α-motoneurons in the spinal cord, the neuromuscular junctions, and the muscle.[25] Therefore, an increase in CSE measured by TMS could be due to changes at any or all of these structures. However, spinal mechanisms are unlikely to mediate the increases in CSE after acute ST.[6] Previous studies showed that ST intensity affected CSE but not spinal excitability measured by cervicomedullary electrical stimulation.[6] Furthermore, increases in corticospinal transmission and/or α-motoneuron excitability after acute ST are not always present.[26] For that reason, mechanisms other than spinal changes were proposed to explain the increases in CSE after acute ST. Increases in corticospinal neuron excitability or reductions in the efficacy of the intracortical inhibitory circuits can both increase the efficacy of the excitatory input to α-motoneurons thereby increasing the response to TMS. However, we found no reductions in GABAa or GABAb receptor–mediated cortical inhibition.

Although two-way RM-ANOVA revealed a nonsignificant interaction between factors for SICI ($P = .09$, $\eta_p^2 = 0.17$), paired comparisons showed a small increase in SICI (ie, reduced CS/TS ratio) after 75% of MVC ST session (from 76.8% to 69.1% of TS, $P = .01$, ES = −0.26, 95.0% CI = −0.41, −0.13). This small increase in SICI after high-intensity acute ST could be related to a methodological issue, that is, the test pulse MEP size. The amount of inhibition increases with increasing test pulse MEP size.[27] Because we used PRE

stimulation intensity during the POST measurements, the increase in the test pulse MEP size after high-intensity ST could have led to the slight, nonsignificant increase in SICI. Although this could be viewed as a limitation, the efficacy of SICI is related to the population of cortical circuits activated by the test pulse.[28] The variable that determines which circuits are activated by TMS is the stimulation intensity and not changes in excitability.[28] Therefore, reductions in stimulation intensity to adjust the test pulse size after a ST session could act as a confounding factor by affecting the cortical circuits activated the test stimulus and reducing the estimates of SICI because of a higher contribution of early indirect waves to the MEP, which are less affected by intracortical inhibition. Future studies should include both approaches (adjusted and not adjusted test pulse size) to further understand the effects of an acute ST session on SICI. Notwithstanding, the small increases in SICI in the present study partially agree with those from a recent meta-analysis showing that SICI is not modulated consistently following a single session of ST,[29] which could be also related to different approaches used to measure SICI after a single session of ST (adjusted and not adjusted TS size).

Regarding SP, past results have been inconsistent with studies showing increases set by set during an ST session[14] and decreases[15] after an acute ST session. Here, we found no change after unilateral acute ST at a low or high intensity. These results combined with the SICI data suggest that, although chronic ST could lead to reductions in SICI and SP,[12] just a single session of isometric ST does not reduce the efficacy of the GABAa and GABAb receptor–mediated inhibitory intracortical circuits projecting to the cortical excitatory neurons. Acute reductions in intracortical inhibition could be a compensatory mechanism to diminish the effect of peripheral fatigue on force output.[15] However, the ramped isometric contractions we used did not require participants to hold the target force, minimizing any peripheral fatigue (discussed below). Therefore, acute modifications in the efficacy of the inhibitory intracortical circuits could be more related to the level of peripheral fatigue attained during the training session than to the intensity of training.[15] Also, other ST characteristics could influence the acute modulation of the responses to TMS after a single session of ST. For example, dynamic ST paced by an audible cue leads to increased CSE accompanied by increased ICF and reduced intracortical inhibition, whereas internally paced ST did not.[30] This greater acute neural modulation could be related to higher auditory afferent input from the auditory cortex synchronized with the activation of corticospinal neurons during muscle contractions, which lead to an increased synaptic efficacy according to Hebbian principles.[31] Thus, it seems that the acute neural modulation after an acute ST session could be affected by different ST characteristics such as intensity, level of peripheral fatigue, the type of contraction or the strategy of pacing the movement, or even the volume of exercise.

Therefore, combined results from the present and past studies[6] suggest that spinal mechanisms or changes in intracortical circuits are not the main mechanisms underlying the acute increase in CSE after an acute bout of ST. Then, it is likely that the increases in the net excitatory output from cM1 to the muscle after an acute bout of ST are related to changes in the membrane excitability of the corticospinal neurons receiving input from the corticocortical neurons activated by the single-pulse TMS.

A methodological difference between the present and past studies is that we measured corticospinal changes at 5% or 25% background MVC and not at rest. Measuring responses to TMS during contraction represents more faithfully the adaptations that occur during training compared with the same measures obtained at rest.[32] The increased MEP size after training during contraction could thus reflect plasticity associated with the task unlike the CSE measured at rest. Nevertheless, we found that a session of high-intensity but not low-intensity ST increased the CSE of the trained arm when measured during 5% of MVC contractions to a similar extent as when CSE was measured at rest in previous studies[6] (+47% during contraction vs +76% at rest). The differences in the magnitude of change between both studies[6] could be related to differences in the size of the baseline MEPs (7.05% of M_{max} vs 4.57% of M_{max}). However, in both studies the absolute increase was similar (to a 10% vs to a 8% of M_{max}). This suggests that the increased responses to TMS after training have not became more facilitated by the muscle contraction compared with rest, suggesting that acute changes after ST occurred in the intrinsic properties of the cortical neurons that could be already measured at rest. Nevertheless, we did not find any increases in CSE when measured during 25% of MVC contractions. MEP size in BB tends to be progressively facilitated up to a 40%-50% of MVC.[33] However, independent of contraction intensity, MEP size tends to peak at an amplitude around 60%-70% of M_{max}.[33] Therefore, a lack of change in MEPs during 25% of MVC after the high-intensity ST session could be related to the high baseline size of MEPs (~50%). The fact that baseline MEPs were already close to its maximum means that single-pulse TMS before training already recruited almost all of the excitable cortical neurons, limiting the scope for further increases. Also, because measurements were obtained during contractions, it is unknown whether spinal changes would have behaved in a similar manner as at rest.[6] Therefore, a direct comparison with previous studies is not possible and we cannot discard a concomitant increase in α-motoneuron excitability contributing to the increase in CSE after high-intensity acute ST seen here. However, short-term ST periods have failed to produce adaptations at

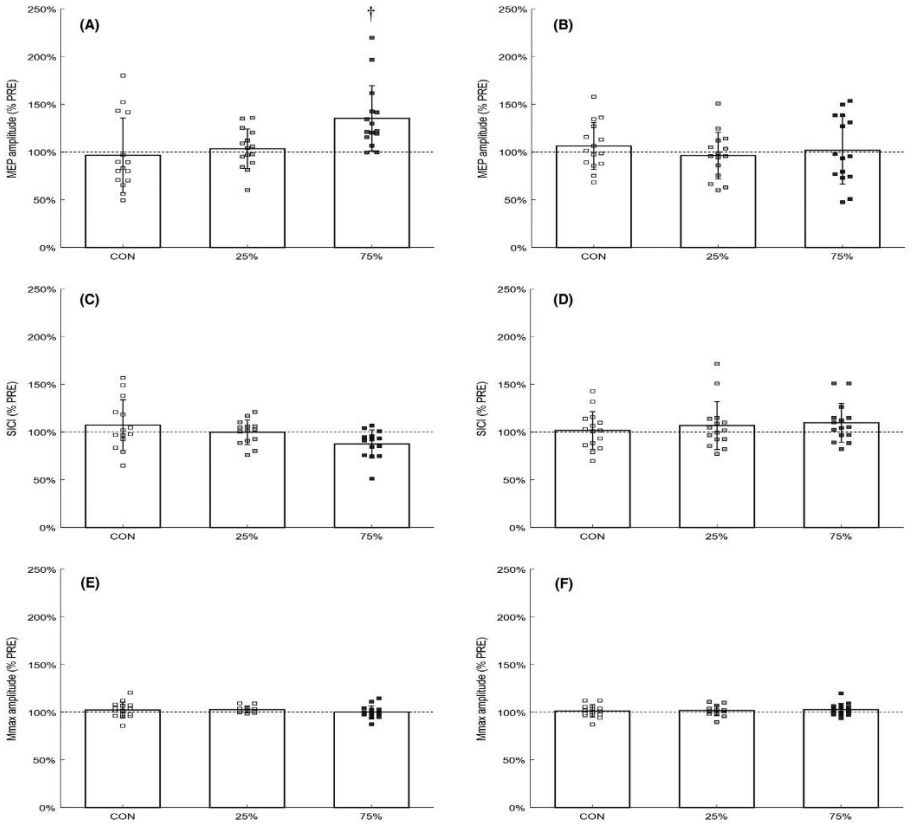

FIGURE 2 $MEP_{5\%}/M_{max}$, M_{max}, and SICI change after strength training (n = 15). Left panel shows the change (mean ± SD) in the $MEP_{5\%}/M_{max}$ (A), SICI (C), and M_{max} (E) of the right trained BB after the ST sessions performed at 25% and 75% of the MVC and the CON condition. Right panel shows the change (mean ± SD) in the $MEP_{5\%}/M_{max}$ (B), SICI (D), and M_{max} (F) of the left untrained BB after the ST sessions performed at 25% and 75% of the MVC and the CON condition. (†) shows a statistically significant difference ($P < .05$) to PRE values

the spinal level measured by cervicomedular electrical stimulation[34] and H reflexes.[35] This strengthens the support for the hypothesis that short-term increases in α-motoneuron discharge rate that lead to increases in MVC force are mediated by increases in the net excitatory input to the α-motoneuron pool from supraspinal centers.[36]

Because we did not measure MVC force after ST, we cannot discard the possibility that fatigue has influenced our results. However, there is indirect evidence to suggest that fatigue was low or altogether absent. For example, we found no changes in the pre-stimulus rmsEMG, suggesting that any increase in neural drive was needed to maintain the force output as a consequence of reductions in muscle or α-motoneuron excitability. Also, in a previous study with an identical training, resting M_{max} -associated twitch forces did not decrease during the 30 minutes after the intervention, suggesting that there were no reductions in muscle contractile properties as a consequence of fatigue.[6] Another factor that can potentially influence our results is central fatigue. The best indicator for the assessment of central fatigue is voluntary activation. Unfortunately, we did not measure voluntary activation in this study. However, as intracortical inhibition did not increase, we assume that central fatigue was low or altogether absent.

4.2 | Untrained side

The central nervous system adapts quickly to motor practice in the trained and the untrained muscle.[37] Therefore, several studies have examined whether the acute changes occurring after a single session of unilateral ST in the trained hemisphere[4-6,14,15] would also occur in ipsilateral, untrained brain structures.[7,21] Notwithstanding, results from those studies are contradictory, with one study showing increases in CSE and reductions in SICI after a session of dynamic ST,[7] whereas another study reported no effects of an acute unilateral isometric ST session on CSE, SICI, ICF, and IHI of the untrained hemisphere.[21] Our results agree with these latter data, showing no effects of a single session of isometric unilateral ST of the elbow flexors on TMS outcomes in iM1. Furthermore, despite cross-sectional studies demonstrating that iM1 excitability increases and intracortical inhibition decreases more during high- compared with low-intensity contractions,[19,22] our results revealed no intensity effects on the responses to TMS in iM1 after a single session of unilateral isometric ST.

Discrepancies between the effects of a session of unilateral ST on iM1 could be related to the type of contractions used during training. Eccentric compared with concentric contractions activate iM1 more strongly.[38] This higher cross-activation is probably a consequence of the greater neural resources needed for programming and planning eccentric compared with static or concentric contractions,[39] or related to inhibitory and facilitatory influences from the dorsal premotor and posterior parietal cortices in the cM1 and iM1.[40] Another important aspect with regard to cross-activation is the intensity of a contraction. It is known that contractions need to be at moderate-high intensity to result in cross-activation of the ipsilateral hemisphere.[19,22] The slowly ramped isometric contractions used in the current study result in relatively short periods of contractions at moderate-high intensity (>50% MVC). These short periods at moderate-high intensity might in turn have resulted in limited cross-activation during the contractions, reducing the scope for modulation of the corticospinal tract projecting to the untrained BB. Therefore, the absence of changes in iM1 after a unilateral isometric ST session could be related to an insufficient level of cross-activation during progressive isometric contractions, compared with unilateral dynamic ST mixing high-intensity eccentric and concentric contractions.

Therefore, although iM1 adaptations occur after chronic periods of ST,[1,20,21] even with isometric contractions,[21] the time course of those adaptations is longer than a single session, even if the intensity of ST is high. Indeed, previous studies showed that interlimb transfer of voluntary force and correlated increases in iM1 excitability to occur might require at least 10 sessions or 500 isometric contractions.[21] Therefore, it is not possible to infer the long-term effectiveness of different ST configurations (ie, intensity and volume) based on the effects of just one session of ST. Consequently, longitudinal studies will be needed to determine the effectiveness of different ST configurations on iM1 plasticity. Furthermore, acute and chronic changes may occur in other ipsilateral structures that single-coil TMS cannot probe that are also bilaterally activated during unilateral contractions, such as supplementary motor area, sensory regions, prefrontal, premotor, cingulate, and parietal cortices, or cerebellum.[18]

5 | CONCLUSIONS

High- but not low-intensity isometric ST of the elbow flexors increased CSE in the BB when measured at a background MVC of 5%. However, such increases were not accompanied by decreases in intracortical inhibition or increases in intracortical facilitation. These results suggest that increases in corticospinal neurons or α-motoneuron excitability are the main mechanisms underlying the increases in CSE. In contrast, no effects on CSE and intracortical circuitry occurred in the untrained hemisphere, suggesting that more than one session of unilateral isometric ST is needed to evoke adaptations in the untrained corticospinal tract independent of training intensity.

6 | PERSPECTIVES

Peripheral and neural adaptations to ST have different time courses. Adaptations in the central nervous system usually precede changes in the muscle and tend to underlie most of the early gains in MVC force. Therefore, it is important for coaches training healthy individuals and also patients with neuromuscular conditions or older adults, to know how modifications in training variables, such as training intensity, could affect early adaptations to ST. We show that training intensity is a key determinant of the acute increases in cortical or α-motoneuron excitability occurring in the early stages of training, which could explain the better effectiveness of chronic high-intensity ST in producing MVC force increases. However, just one session of unilateral isometric ST does not lead to acute changes in the iM1.

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CONFLICT OF INTEREST
None of the authors declare conflict of interest.

ORCID
David Colomer-Poveda https://orcid.org/0000-0002-1064-2803

Gonzalo Márquez https://orcid.org/0000-0002-2305-5229

REFERENCES

1. 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.
2. Weier AT, Pearce AJ, Kidgell DJ. Strength training reduces intracortical inhibition. *Acta Physiologica*. 2012;206(2):109-119.
3. Aagaard P, Simonsen EB, Andersen JL, Magnusson P, Dyhre-Poulsen P. Neural adaptation to resistance training: changes in evoked V-wave and H-reflex responses. *J Appl Physiol*. 2002;92(6):2309-2318.
4. Selvanayagam VS, Riek S, Carroll TJ. Early neural responses to strength training. *J Appl Physiol*. 2011;111(2):367-375.
5. Nuzzo JL, Barry BK, Gandevia SC, Taylor JL. Acute strength training increases responses to stimulation of corticospinal axons. *Med Sci Sports Exerc*. 2016;48(1):139-150.
6. Colomer-Poveda D, Romero-Arenas S, Lundbye-Jensen J, Hortobagyi T, Marquez G. Contraction intensity-dependent variations in the responses to brain and corticospinal tract stimulation after a single session of resistance training in men. *J Appl Physiol*. 2019;127(4):1128-1139.
7. Leung M, Rantalainen T, Teo WP, Kidgell D. Motor cortex excitability is not differentially modulated following skill and strength training. *Neuroscience*. 2015;305:99-108.
8. Chen R. Interactions between inhibitory and excitatory circuits in the human motor cortex. *Exp Brain Res*. 2004;154(1):1-10.
9. Nakamura H, Kitagawa H, Kawaguchi Y, Tsuji H. Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. *J Physiol*. 1997;498(Pt 3):817-823.
10. Kujirai T, Caramia MD, Rothwell JC, et al. Corticocortical inhibition in human motor cortex. *J Physiol*. 1993;471:501-519.
11. Inghilleri M, Berardelli A, Cruccu G, Manfredi M. Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. *J Physiol*. 1993;466:521-534.
12. Kidgell DJ, Bonanno DR, Frazer AK, Howatson G, Pearce AJ. Corticospinal responses following strength training: a systematic review and meta-analysis. *Eur J Neuorsci*. 2017;46(11):2648-2661.
13. Latella C, Hendy AM, Pearce AJ, VanderWesthuizen D, Teo WP. The time-course of acute changes in corticospinal excitability, intra-cortical inhibition and facilitation following a single-session heavy strength training of the biceps brachii. *Front Hum Neurosci*. 2016;10:607.
14. Ruotsalainen I, Ahtiainen JP, Kidgell DJ, Avela J. Changes in corticospinal excitability during an acute bout of resistance exercise in the elbow flexors. *Eur J Appl Physiol*. 2014;114(7):1545-1553.
15. Latella C, Teo WP, Harris D, Major B, VanderWesthuizen D, Hendy AM. Effects of acute resistance training modality on corticospinal excitability, intra-cortical and neuromuscular responses. *Eur J Appl Physiol*. 2017;117(11):2211-2224.
16. Keller A. Intrinsic synaptic organization of the motor cortex. *Cereb Cortex*. 1993;3(5):430-441.
17. Ortu E, Deriu F, Suppa A, Tolu E, Rothwell JC. Effects of volitional contraction on intracortical inhibition and facilitation in the human motor cortex. *J Physiol*. 2008;586(Pt 21):5147-5159.
18. Dai TH, Liu JZ, Sahgal V, Brown RW, Yue GH. Relationship between muscle output and functional MRI-measured brain activation. *Exp Brain Res*. 2001;140(3):290-300.
19. Perez MA, Cohen LG. Mechanisms underlying functional changes in the primary motor cortex ipsilateral to an active hand. *J Neurosci*. 2008;28(22):5631-5640.
20. Zult T, Goodall S, Thomas K, Solnik S, Hortobagyi T, Howatson G. Mirror training augments the cross-education of strength and affects inhibitory paths. *Med Sci Sports Exerc*. 2016;48(6):1001-1013.
21. Hortobagyi T, Richardson SP, Lomarev M, et al. Interhemispheric plasticity in humans. *Med Sci Sports Exerc*. 2011;43(7):1188-1199.
22. Hortobagyi T, Taylor JL, Petersen NT, Russell G, Gandevia SC. Changes in segmental and motor cortical output with contralateral muscle contractions and altered sensory inputs in humans. *J Neurophysiol*. 2003;90(4):2451-2459.
23. Kimberley TJ, Borich MR, Prochaska KD, Mundfrom SL, Perkins AE, Poepping JM. Establishing the definition and inter-rater reliability of cortical silent period calculation in subjects with focal hand dystonia and healthy controls. *Neurosci Lett*. 2009;464(2):84-87.
24. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med*. 2016;15(2):155-163.
25. Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. *Lancet Neurol*. 2003;2(3):145-156.
26. Nuzzo JL, Barry BK, Gandevia SC, Taylor JL. Effects of acute isometric resistance exercise on cervicomedullary motor evoked potentials. *Scand J Med Sci Sports*. 2018;28(5):1514-1522.
27. Daskalakis ZJ, Christensen BK, Fitzgerald PB, Roshan L, Chen R. The mechanisms of interhemispheric inhibition in the human motor cortex. *J Physiol*. 2002;543(Pt 1):317-326.
28. Garry MI, Thomson RH. The effect of test TMS intensity on short-interval intracortical inhibition in different excitability states. *Exp Brain Res*. 2009;193(2):267-274.
29. Mason J, Frazer A, Pearce A, et al. Determining the early corticospinal-motoneuronal responses to strength training: a systematic review and meta-analysis. *Rev Neurosci*. 2018;30(5):463-476.
30. Mason J, Howatson G, Frazer AK, et al. Modulation of intracortical inhibition and excitation in agonist and antagonist muscles following acute strength training. *Eur J Appl Physiol*. 2019;119(10):2185-2199.
31. Jantzen KJ, Steinberg FL, Kelso JA. Coordination dynamics of large-scale neural circuitry underlying rhythmic sensorimotor behavior. *J Cogn Neurosci*. 2009;21(12):2420-2433.
32. Beck S, Taube W, Gruber M, Amtage F, Gollhofer A, Schubert M. Task-specific changes in motor evoked potentials of lower limb muscles after different training interventions. *Brain Res*. 2007;1179:51-60.
33. Pearcey GEP, Power KE, Button DC. Differences in supraspinal and spinal excitability during various force outputs of the biceps brachii in chronic- and non-resistance trained individuals. *PLoS ONE*. 2014;9(5):e98468.
34. Nuzzo JL, Barry BK, Jones MD, Gandevia SC, Taylor JL. Effects of four weeks of strength training on the corticomotoneuronal pathway. *Med Sci Sports Exerc*. 2017;49(11):2286-2296.
35. Giboin LS, Weiss B, Thomas F, Gruber M. Neuroplasticity following short-term strength training occurs at supraspinal level and is specific for the trained task. *Acta Physiol Physiologica*. 2017;222(4):e12998.

36. Del Vecchio A, Casolo A, Negro F, et al. The increase in muscle force after 4 weeks of strength training is mediated by adaptations in motor unit recruitment and rate coding. *J Physiol*. 2019;597(7):1873-1887.
37. Lee M, Hinder MR, Gandevia SC, Carroll TJ. The ipsilateral motor cortex contributes to cross-limb transfer of performance gains after ballistic motor practice. *J Physiol*. 2010;588(Pt 1):201-212.
38. Howatson G, Taylor MB, Rider P, et al. Ipsilateral motor cortical responses to TMS during lengthening and shortening of the contralateral wrist flexors. *Eur J Neuorsci*. 2011;33(5):978-990.
39. Fang Y, Siemionow V, Sahgal V, Xiong F, Yue GH. Greater movement-related cortical potential during human eccentric versus concentric muscle contractions. *J Neurophysiol*. 2001;86(4):1764-1772.
40. Koch G, Fernandez Del Olmo M, Cheeran B, et al. Focal stimulation of the posterior parietal cortex increases the excitability of the ipsilateral motor cortex. *J Neurosci*. 2007;27(25):6815-6822.

SUPPORTING INFORMATION

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

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