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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

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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

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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).

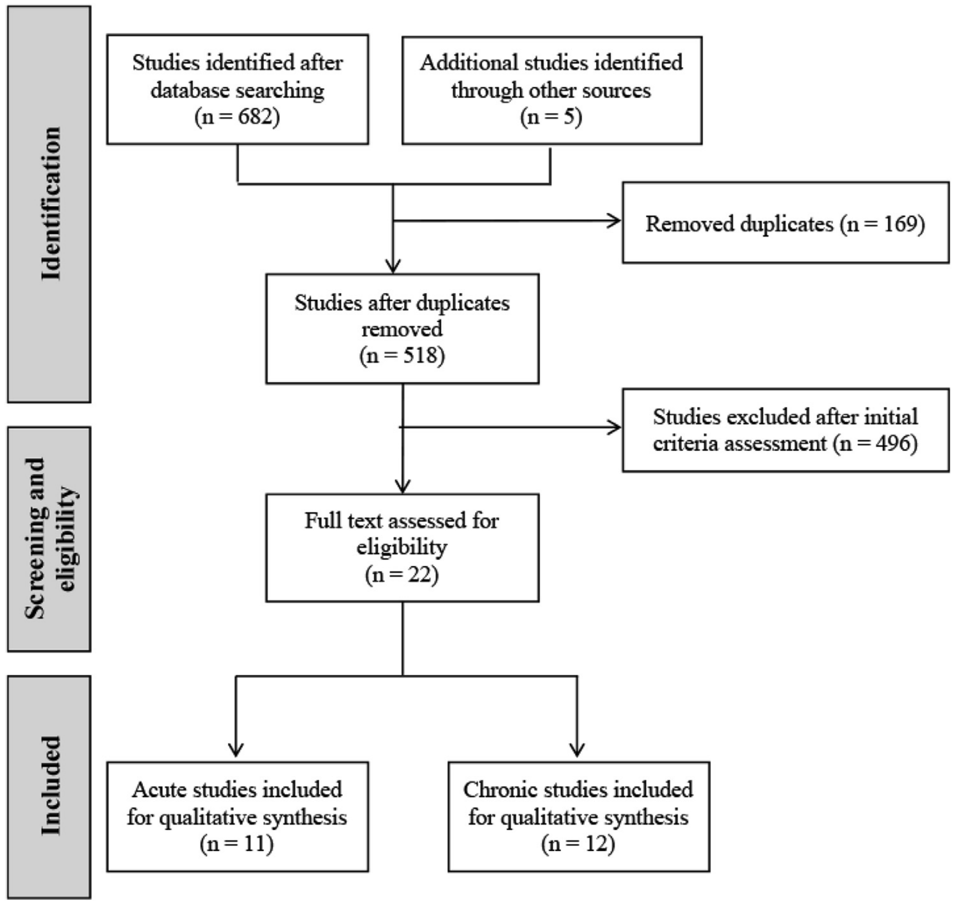

Fig. 1. Flow diagram of studies identified, excluded, and included in the systematic review.

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. Experiment 2: Same intervention (same volume) without fatigue with 5% MVC contractions.		CSE, SICI, and ICF at rest CSE, SICI, and ICF at rest	CSE and SICI: ↔ ICF: ↓* 96% after 2–6 min ↔ after 15–19 min CSE, SICI, and ICF: ↔	Fair
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 Experiment 2: Until 25% of time to exhaustion	CSE at rest CSE at rest	↓* 60.6 ± 4.9% after 10–18 min. ↔ after 40 min ↔ Just after. ↑* 166.5 ± 4.6% after 10 min–60 min.	Fair
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) Resistance trained subjects (n = 8) Endurance trained subjects (n = 8)	CSE at rest CSE at rest CSE at rest	↓* 38-27% during the first 20 min ↓* 53-26% during the first 30 min ↓* 47-38% during the first 10 min	Fair
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 Control group (n = 8): Without training		CSE, SICI, IHI, and ICF at rest. CSE, SICI, IHI, and ICF at rest.	CSE, SICI, and ICF: ↔ IHI: ↓* 8.9% CSE, SICI, and ICF: ↔ IHI: ↓* 1.8%	6
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 Control condition with no training		CSE during contraction CSE during contraction	CSE: ↔ CSE: ↔	6
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). Control condition with no training		CSE at rest CSE at rest	CSE: ↔ CSE: ↔	6
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 Self-paced (n = 11): Dominant elbow flexion: 4 sets × 6–8 reps at 70–80% of 1-RM. Tempo: Preferred tempo Control group (n = 10): Without training		CSE and SICI during contraction CSE and SICI during contraction CSE and SICI during contraction	CSE: ↑* 43.3 ± 4.9% SICI: ↓* 20.3 ± 4.6% CSE and SICI: ↔ CSE and SICI: ↔	6

*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

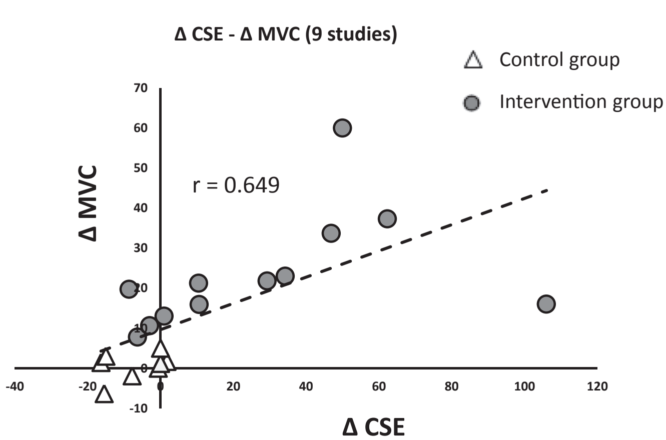

Fig. 2. Correlation between changes in ipsilateral corticospinal excitability and maximal voluntary force of the untrained limb.

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.

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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