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Review article

Corticospinal adaptations following resistance training and its relationship with strength: A systematic review and multivariate meta-analysis

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A R T I C L E I N F O

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A B S T R A C T

Neural adaptations to resistance training (RT) and their correlation with muscle strength remain partially understood. We conducted a systematic review and multivariate meta-analysis to examine the effects of metronome-paced (MP), self-paced (SP), and isometric (IM) training on M1 and corticospinal pathway activity. Following MP RT, a significant increase in corticospinal excitability was observed, correlating with increased strength. Conversely, no significant relationship was found after SP or IM training. RT also reduced the duration of the cortical silent period, but this change did not predict strength changes and was not specific to any training modality. No significant effects were found for short-interval intracortical inhibition. Our findings suggest that changes in corticospinal excitability may contribute to strength gains after RT. Furthermore, the relationship between these adaptations and strength appears dependent on the type of training performed.

1. Introduction

Resistance training (RT) has been described as a safe form of exercise for athletes and non-athletic individuals alike (Granacher et al., 2016). RT is also recognized as beneficial for people suffering from various conditions, such as stroke (Wist et al., 2016). RT refers to specialized physical conditioning methods that apply a variety of resistance loads, different movement speeds, and various training methods, including weight machines, free weights (barbells and dumbbells), elastic bands, medicine balls, and plyometrics (Faigenbaum and Myer, 2010). Regular RT results in increases in both strength and muscle fiber cross sectional area, although these adaptations may occur over weeks to years (Balagopal et al., 2001; Hasten et al., 2000). However, it has been suggested that increased strength is not solely attributable to muscle hypertrophy and that other mechanisms such as neural adaptations could be involved (Gabriel et al., 2006; Hortobágyi et al., 2021).

Transcranial magnetic stimulation and peripheral nerve stimulation studies have described neural adaptations to RT, among others, in the intracortical inhibitory circuits, corticospinal tract, or spinal circuitry (Carroll et al., 2009; Christie and Kamen, 2014, 2010; Coombs et al., 2016; Goodwill et al., 2012; Griffin and Cafarelli, 2007; Hendy and Kidgell, 2013; Hortobágyi et al., 2009; Hortobágyi and Maffiuletti, 2011; Iglesias-Soler et al., 2016; Jensen et al., 2005; Kidgell and Pearce, 2010; Latella et al., 2012; Lee et al., 2009; Manca et al., 2016; Mason et al., 2020, 2019, 2017; Pearce et al., 2013; Siddique et al., 2020a; Weier et al., 2012). However, there is some disparity as to whether RT leads to homogeneous neural adaptations. To date, two meta-analyses have attempted to address this question (Kidgell et al., 2017; Siddique et al., 2020b), concluding that RT induces large and consistent changes in intracortical inhibition and the cortical silent period (with a decreasing effect in both cases), while a modest and heterogeneous effect has been reported for corticospinal excitability measures. Both meta-analyses also reported that RT involved some corticospinal adaptations that could contribute to a training-related increase in muscle strength. However, no formal analysis to date has been conducted to assess this relationship.

Another interesting point to analyze that has not been addressed in previous meta-analyses is the relationship between RT exercise modality and increased strength and corticospinal excitability. Studies included in previous quantitative reviews can be classified according to three different modalities of RT, depending on the type of contraction involved in the exercise: metronome-paced (MP), self-paced (SP), or

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isometric (IM). MP exercise involves the performance of concentric and eccentric repetitions following a specific timing for each phase paced externally by a metronome (Siddique et al., 2020a). SP exercise consists of performing repetitions in a free-timing mode, that is, without setting any time for concentric or eccentric phases. Finally, IM exercise involves holding a certain weight at a specific angle of contraction for a set time interval or holding a specific force against an immovable/fixed object. This difference in RT exercise modality could lead to different effects both in the central nervous and musculoskeletal systems, as well as in the possible interaction between them. This hypothesis has not been thoroughly investigated except for a few studies in which neural and muscular adaptations of different exercise modalities are compared using an experimental approach (Leung et al., 2017; Siddique et al., 2020a).

The current study aimed to address questions that were not answered in previous systematic reviews and meta-analyses. By means of multivariate meta-analytic techniques, we sought to elucidate the direction of the relationship between corticospinal excitability and corticospinal inhibition with strength, assessing to what extent training-induced changes in corticospinal excitability may depend on the type of exercise performed (MP, SP or IM) and whether this correlation conditions the effects on muscle strength. In addition, we analyzed the possible impact on the outcome variables of the limb trained (upper or lower).

2. Materials and methods

2.1. Search strategy and selection of studies

A systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). The search was conducted using the following databases: PubMed, Scopus, Web of Science, SPORTDiscus, Cochrane Library, EMBASE, and ScienceDirect, from inception until August 28, 2022. The search strategy for this meta-analysis is provided as supplementary material (Suppl. Material, Fig. 1). A set of independent variables ("muscle strength," "strength," and "resistance training") and dependent variables ("transcranial magnetic stimulation," "TMS," "corticospinal excitability", "cortical inhibition", "motor evoked potential", "corticospinal inhibition", "silent period" and "short interval intracortical inhibition") were defined. The groups studied included untrained individuals who underwent different modes of training (MP, SP, or IM) and excluded patients with any kind of pathology, injury, or disease. References included in previous reviews and meta-analyses were also evaluated.

2.2. Inclusion and exclusion criteria

We required that articles meet the following criteria to be included in the review: (1) peer-reviewed publications, written in English; (2) including healthy untrained subjects of both sexes with an age range from 18 to 45; (3) evaluating at least one experimental group that underwent resistance or strength training between two and four weeks in duration; (4) the load applied during RT involved more than 50% maximal voluntary contraction (MVC); (5) including a control group compared to the experimental group(s), and (6) assessing post-training changes in at least one of the following measures obtained by single or paired pulse TMS applied at M1: motor evoked potentials (MEP), corticospinal silent period (CSP), or short-interval intracortical inhibition (SICI). These measures should be measured together with changes in muscle strength in the same subject. Fatigue studies (i.e., studies measuring the recovery time of TMS values immediately after finishing a single exhaustive training session) were excluded, as were studies that performed skill or visual training (such as mental exercises) rather than RT. Studies using other non-invasive brain stimulation techniques such as direct transcranial stimulation in combination with RT were also discarded.

2.3. Data extraction

Motor cortex excitability can be objectively measured as a MEP (Reis et al., 2008). MEP amplitude is defined as the electromyographic (EMG) response of the electric current generated in a specific area of M1 produced by the magnetic field of the TMS coil after the delivery of a single pulse. Peak-to-peak MEP amplitude analysis is a common procedure in assessing the baseline state of motor cortex excitability and whether it increases or decreases following a specific intervention, such as RT (Amassian et al., 1998; Chen et al., 2008; Rothwell, 1997; Thut et al., 2003). Twelve studies measured peak-to-peak MEP amplitude (Christie and Kamen, 2014; Griffin and Cafarelli, 2007; Hendy and Kidgell, 2013; Hortobágyi et al., 2009; Iglesias-Soler et al., 2016; Jensen et al., 2005; Kidgell and Pearce, 2010; Latella et al., 2012; Lee et al., 2009; Pearce et al., 2013; Kidgell et al., 2010; Leung et al., 2013). Eight studies (Carroll et al., 2009; Coombs et al., 2016; Goodwill et al., 2012; Leung et al., 2017; Manca et al., 2016; Mason et al., 2017; Pearce et al., 2013; Weier et al., 2012) provided measures of properties obtained in the MEP input-output curve (eg, the area under the recruitment curve). Some recent studies indicate that analysis of these properties is more informative and reliable as a measure of corticospinal excitability than analysis of single-point measurements (Carson et al., 2013). Given that the descriptor variables of the input-output curve properties varied extensively from study to study, in these cases, an average of all points of the MEP input/output curve was extracted and used as a single indicator for the meta-analysis.

Other methods based on the analysis of the duration of CSP or paired pulse protocols (e.g., SICI) provide valuable information to assess neural adaptations in the motor cortex following RT (Kidgell et al., 2017; Siddique et al., 2020b). SICI was assessed to examine intracortical inhibition, being calculated as the ratio of the conditioned to unconditioned MEP (Kujirai et al., 1993). CSP was recorded as the period of time without EMG muscle activity after MEP stimulus during voluntary muscle activation (Orth and Rothwell, 2004). Both SICI and CSP provide information about the effect of RT at the GABA-ergic system (Kidgell et al., 2017). MVC was determined as the maximum weight the subject could lift in a single maximum contraction (Leung et al., 2017). Data were extracted directly from text or tables, or from graphs using WebPlotDigitizer (Rohatgi, 2020).

In addition, a standardized form was used to extract the following data: authors, publication date, study design, type and duration of RT, and sampling procedure. Other variables collected included the number of participants per group, the percentage of males, age, and the limb where MVC and TMS were analyzed (upper or lower).

2.4. Quality and risk-of-bias assessment

The Downs and Black checklist (Downs and Black, 1998) was used to assess the methodological quality of the studies included in our review. This checklist can be applied to both randomized and nonrandomized studies. The Cochrane Risk-of-Bias tool for randomized trials (RoB 2) (Borenstein et al., 2010; Higgins et al., 2019) was also used to assess the risk of bias for the studies included in our meta-analysis. This tool is structured into five domains of bias: (1) arising from the randomization process; (2) in selection of the reported result; (3) in measurement of the outcome; (4) due to missing outcome data, and (5) due to deviations from intended interventions. A rating of "low" or "high" risk of bias was assigned for each criterion. Where there were insufficient details reported about the criterion, the risk of bias was defined as an "unclear risk of bias."

2.5. Statistical analysis

Effect sizes were estimated using a sample estimator for the design of the pretest-posttest-control group (d_{ppc2}), using equation 8 in Morris et al., (Morris, 2008) which estimates the population standard deviation by combining the pretest standard deviations of the training and control groups. For this estimation, the pretest-posttest correlation was set at 0.7 (Rosenthal, 1991). A sensitivity analysis was performed repeating the meta-analysis, setting this correlation at 0.5 and 0.9. The direction of the effect sizes was coded such that a positive effect size would reflect an increase in the strength, an increase in MEP amplitude, an increase in the duration of the CSP, or a decrease in SICI, for the training group compared to the control group (pretest-posttest change compared to control). We counted each study as one, although for the statistical analysis, data was extracted separately for each intervention group. In three articles, there was a single control group for more than one intervention group. To correct for the bias such "double counting" could generate, the number of control subjects in these trials was divided by two (Van Middelkoop et al., 2011).

We then conducted a multivariate meta-analysis using the structural equation modeling approach (Cheung, 2008). A multivariate random-effects model was used to jointly estimate the effect sizes in the TMS measures and muscle strength, as implemented in the "metaSEM" R package (Cheung, 2014). This approach also allowed us to study the degree of dependence (correlation) between the two outcomes. Given that sampling covariances (or correlations) between changes in TMS measures and strength were not available in most studies, we used the sampling correlation between changes in MEP/SICI and strength reported by Siddique et al., (Siddique et al., 2020a) who observed correlations for each of the three types of RT under study. For the case of CSP, we used the sampling correlation between changes in CSP and strength reported by Christie & Kamen (Christie and Kamen, 2014). We then approximated the covariance of study k using the following formula (Schwarzer et al., 2015):

$$\widehat{Cov}(\theta_1, \theta_2) = SE_{\theta 1} \times SE_{\theta 2} \times \widehat{\rho}_{1,2}$$

We performed a Cochran Q test of heterogeneity on fitted multivariate meta-analytical models (Gasparrini et al., 2012). To quantify the heterogeneity of each effect size, we used Higgins' I^2, as implemented in the "metaSEM" package. Here, we established cutoff thresholds corresponding to low (25%), moderate (50%), and high (75%) heterogeneity (Higgins et al., 2003). The estimated covariance matrix ($\widehat{T}^2$) was transformed to a correlation matrix to determine the degree of correlation between the estimated average population effect sizes for the change in MEP amplitude and strength following RT. To test whether the average population effect sizes were significantly different from 0, we fit a new model by setting 0 at both average effect sizes and compared it to the unrestricted model. As these models are nested, a likelihood-ratio test was used for comparison.

Random effect multivariate meta-regression models (through the method of moments) were used to assess the extent to which the heterogeneity was related to study-level factors and specific characteristics (Gasparrini et al., 2012). Potential meta-predictors included training-related variables (type of RT and limb trained). Dummy variables were created to estimate the specific effects of each exercise modality (three levels: SP, IM, and MP) on the two outcomes. All models were fitted using the package R "mixmeta" (Sera et al., 2019).

To test the hypothesis that changes in the TMS variables are predictive of changes in muscle strength after RT, we fit a regression model by regressing the true effect size of the change in strength on the true effect size of the change in the TMS variables. We also fit a mixed-effect moderation analysis to test whether the relationship between changes in motor corticospinal excitability and strength was influenced by exercise modality, which was treated as a moderator. Both models were specified with structural equation models using the OpenMx package (Boker et al., 2011) through the reticular action model specification (McArdle and McDonald, 1984). For these models, we created two latent variables to represent the true effect sizes. All latent and observed variables were then combined. The R^2 index was calculated using Equation 5.30 (Cheung, 2015) to determine the percentage of variance in the true effect size of strength determined by that of the TMS variables. A likelihood-based confidence interval (LBCI) on $R2$ was used to construct the CIs using the "mxCI" function in "'mxModel."

3. Results

3.1. Systematic review

3.1.1. Study selection

The literature search yielded 3408 articles (see Fig. 1 for the PRISMA flow chart of the numbers selected and accepted at each stage of selection). Study characteristics are illustrated in Table 1. All duplicates were removed using EndNote software (Hupe, 2019), reducing the number of studies to 1703. The next step included reading titles and abstracts, which ended with 285 articles to be included in the full text review. Finally, after a thorough reading of the articles, a total of 20 articles were selected.

3.1.2. Characteristics of the studies included

The characteristics of the studies, including articles with only qualitative synthesis analysis (Hortobágyi et al., 2009), are summarized in Table 1. No timeframe was established; however, the studies covered a 16-year period (2005–2022), being that the first work found was from 2005 (Jensen et al., 2005). A total of 435 subjects (229 in training and 206 controls) participated in the 20 studies analyzed; all included studies presented a pre-post design, in which TMS and strength variables were measured before and after resistance training in the same participants. Fourteen were conducted in Australia and 11 of these 14 were performed by the same laboratory (Coombs et al., 2016; Goodwill et al., 2012; Hendy and Kidgell, 2013; Kidgell et al., 2010; Kidgell and Pearce, 2010; Latella et al., 2012; Leung et al., 2017; Mason et al., 2017; Pearce et al., 2013; Weier et al., 2012). Four studies were conducted in the United States, two in Denmark and one in Italy. Sample sizes ranged from 12 to 42 participants from 18 to 35 years old, with an average age of 25. The overall percentage of men represented in the studies was 60%, with 40% women. Fifteen of the studies analyzed focused on upper limb muscles: eight of them on the biceps *brachii*, three on the wrist extensor muscle, three on the first dorsal interosseous, and one in radial deviator. In turn, five studies examined lower limb muscles: three focusing on the quadriceps muscle and two on the *tibialis* anterior muscle. All studies were comprised of a non-athlete population. Participants were in good health with no mental or physical illness.

The studies analyzed three types of RT (MP, SP, and IM). Twelve studies were comprised of MP groups, six included SP groups, and six applied IM RT. Some studies included an analysis of two or three types of RT (MP, SP, or IM) (Coombs et al., 2016; Leung et al., 2017; Siddique et al., 2020a). In those discussing RT with MP, all studies took three seconds in the concentric phase and four seconds in eccentric contraction. In 13 studies the procedure involved three training sessions per week for four weeks; six studies included three training sessions per week for three weeks, and one study had three training sessions per week for two weeks. Only the study by Latella et al. (2012) analyze the effects of RT beyond 4 weeks, providing data for 8 weeks. For the purpose of the meta-analysis, the data from the four-week timepoint of this study was included. Ten studies measured MEP at 10% MVC and 7 measured MEP at 5% MVC, and 3 at rest. Seven studies assessed CSP and eight assessed SICI. Only one study was found that measured SICI in the muscle resting state (Manca et al., 2016). Post-training strength and corticospinal excitability were measured within 48 h after the last training session in 11 studies; 24–48 h after the last training session in five studies; 24–36 h after the last training session in three studies, and 48–96 h after the last training session in one study.

3.1.3. Quality assessment

Following the Downs and Black checklist, the studies assessed ranged between 15 and 19 points (out of 32 possible points) with a mean score

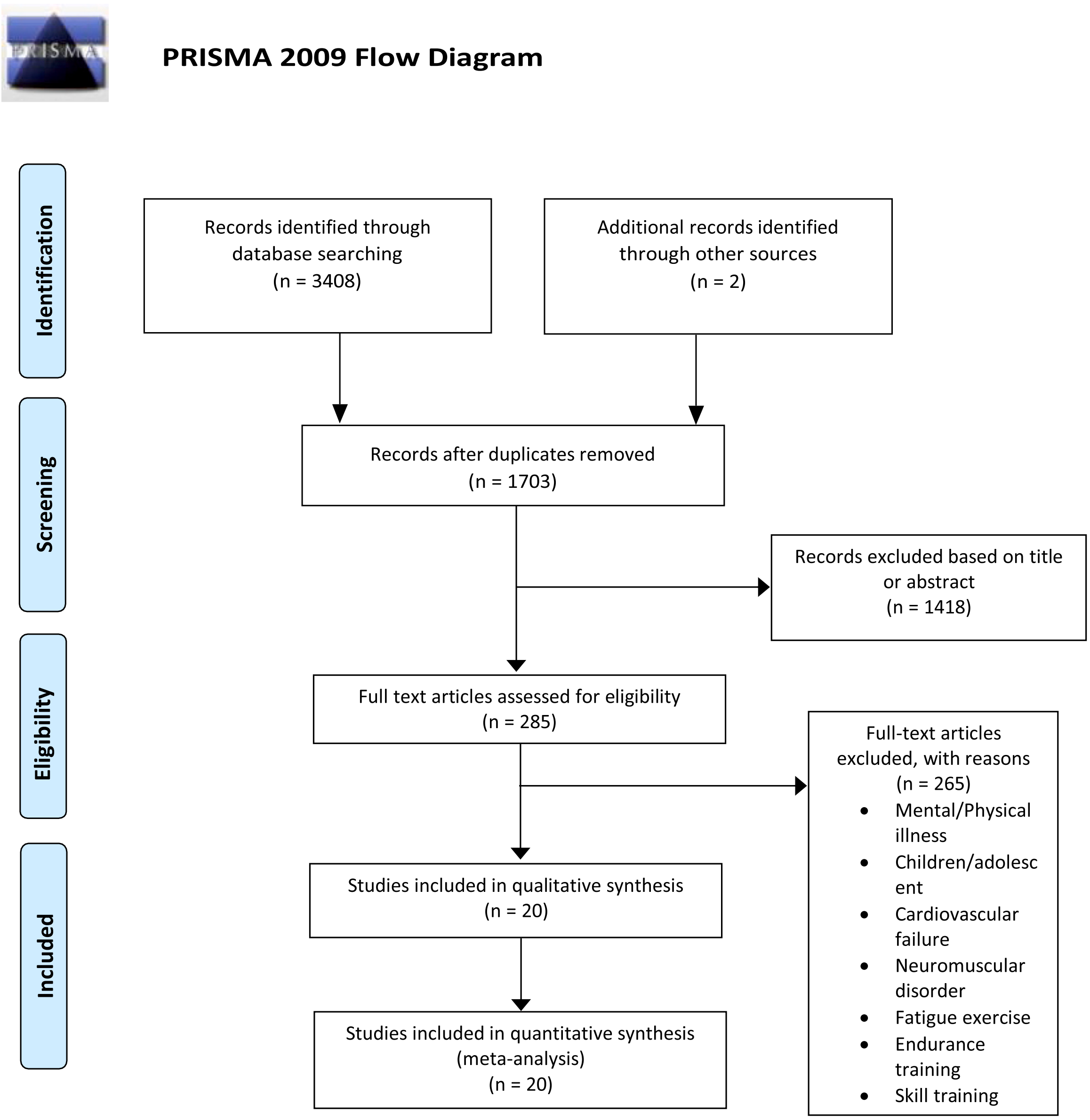

Fig. 1. PRISMA flow diagram.

of 17.73 ± 1.6, indicating low to moderate quality. Many articles were exposed to a high risk of bias in measurement of outcomes and due to deviations from the intended interventions (Fig. 2).

3.2. *Meta-analytical findings*

3.2.1. *Changes in corticospinal excitability and muscle strength*

A random effects model was conducted to estimate the average effect sizes for changes in the MEP amplitude ($\mathrm{SMD}_{\mathrm{MEP}}$) and strength ($\mathrm{SMD}_{\mathrm{strength}}$) after RT. The pooled effect sizes (and approximate 95% Wald CIs) were $\mathrm{SMD}_{\mathrm{MEP}} = 1.03$ (0.44, 1.62), $SE = 0.30$, $p < .001$ and $\mathrm{SMD}_{\mathrm{strength}} = 1.12$ (0.76, 1.49), $SE = 0.19$, $p < .001$. The homogeneity test was statistically significant with $Q(\mathrm{df} = 43) = 221.11$, p < .001. The I^2 for $\mathrm{SMD}_{\mathrm{MEP}}$ and $\mathrm{SMD}_{\mathrm{strength}}$ were.90 and.76, respectively, which is indicative of a high heterogeneity of the estimated effect sizes in the studies. The estimated variance component was $\widehat{T}^2 = \begin{bmatrix} 1.72 & \\ .86 & .56 \end{bmatrix}$. This component was converted to a correlation matrix, resulting in a correlation between the population effect sizes of.87. This value suggests that studies with higher $\mathrm{SMD}_{\mathrm{MEP}}$ tend to report higher $\mathrm{SMD}_{\mathrm{strength}}$. Fig. 3 shows the pooled effect sizes, individual effect sizes, and their 95% confidence ellipse. A sensitivity analysis for MEP amplitude and strength performed repeating the analyses and setting the pretest-posttest correlation at.5 and.9 found that the results did not differ substantially. Results are included in Supplementary Material S2 along with forest plots of univariate random-effects models divided by exercise modality.

To test whether the composite hypothesis that the average effect sizes of the population is equal to 0 (positing that there is no difference with respect to the untrained group), we compared the model obtained with one in which both pooled effect sizes were set at 0. Notably, the multivariate test controls the overall Type I error better in testing the means. The likelihood ratio test (LR) statistic for this model comparison was $\Delta\chi^2(\mathrm{df} = 2) = 23.81$, $p < .001$. Therefore, the null hypothesis that both effect sizes are zero was rejected.

The effects of RT on MEP vary depending on whether they are recorded in the resting or voluntary muscle activation condition, as has been suggested in previous univariate meta-analyses (Kidgell et al., 2017; Siddique et al., 2020b). Three effect sizes recorded at rest were identified (Christie and Kamen, 2014; Jensen et al., 2005; Manca et al., 2016). Next, we fitted the model again by introducing the recording

Table 1
Study characteristics.

Name	Year	Training	Subjects	Sampling	Post-training testing	% MVC at TMS	Results	D & B Score
Jensen et al	2005	Self-paced resistance training of upper limb (biceps brachii). Three training sessions/week during 4 weeks	16 untrained healthy (25 ± 5 years, 9 M & 7 F). Test (n = 8, 4 M & 4 F); Control (n = 8, 5 M & 3 F)	Random	During last training session	Rest	↑ Strength 9%; ↓ MEP/Mmax amplitude 0.9%	17
Griffin & Cafarelli	2006	Isometric resistance training of lower limb (tibial anterior). Three training sessions/week during 4 weeks	20 untrained healthy. (18–32 years, 19 M & 1 F). Test (n = 10); Control (n = 10)	Not-stated	During last training session	10%	↑ Strength 5%; ↑ MEP/Mmax amplitude 4.8%. ↓ SICI 9.8%	17
Carroll et al	2009	Self-Paced resistance training of upper limb (radial deviator muscle). Three training session/week during 4 weeks	17 untrained healthy (19–35 years, 11 M & 6 F). Test (n = 8); Control (n = 9).	Random	2–6 days after last training session	Rest	↑ Strength 22%; ↓ MEP/Mmax amplitude 0.97%	15
Lee et al	2009	Self-paced resistance training of upper limb (wrist abductor). Three training sessiones/week during 4 weeks	23 untrained healthy (18–51 years, 16 M & 7 F). Test (n = 12); Control (n = 11)	Random	48–96 h after last training session	5%	↑ Strength 4.1%; ↓ MEP/Mmax amplitude 8%	18
Hortobagyi et al	2009	Isometric resistance training of upper limb (first dorsal interosseuos). Three training sessions/week during 4 weeks	20 untrained healthy (30.3 ± 1.2 years). Test (n = 10, 8 M & 2 F); Control (n = 10, 8 M & 2 F)	Random	During last training session	5%	↑ Strength 15.6%; ↑ MEP/Mmax amplitude 0.9%	16
Kidgell et al	2010	Metronome-paced resistance training of upper limb (biceps brachii). Three training sessiones/week during 4 weeks	23 untrained healthy. Test (6 M, 20.3 ± 3.4 years, 7 F, 24.4 ± 3.0 years); Control (5 M, 27.6 ± 7.9 years, (5 F, 29 ± 6.2 years)	Random	24–48 h after last training session	10%	↑ Strength 40.9%; ↑ MEP/Mmax amplitude 1.08%. ↓ CSP duration 3 ms	18
Kidgell & Pearce	2010	Isometric resistance training of upper limb (first dorsal interosseuos). Three training sessions/week during 4 weeks	16 untrained healthy (24.12 ± 5.21 years). Test (7 M & 1 F); Control (6 M & 2 F)	Random	During last training session	5%	↑ Strength 22.7%; ↑ MEP/Mmax amplitude 8.6%. ↓ CSP duration 25 ms	18
Goodwill et al	2012	Metrome-paced resistance training of lower limb (rectus femoris). Three training sessions/week during 3 weeks	14 untrained healthy. Test (21 ± 1.1 years, 4 M & 3 F); Control(21 ± 1.2 years, 3 M & 4 F)	Random	During last training session	5%	↑ Strength 48%; ↑ MEP/Mmax amplitude 55.88%. ↓ SICI 9.8%	16
Latella et al	2012	Self-paced resistance training of lower limb (rectus femoris). Three training sessions/week during 4 and 8 weeks	18 untrained healthy (18–35 years, 14 M & 4 F)	Random	Within 48 h following last training session	10%	4 week: ↑ Strength 8.6%; ↑ MEP/ Mmax amplitude 0.5%. ↓ CSP duration 17.7 ms 8 week:	16
Weier et al	2012	Metronome-paced resistance training of lower limb (rectus femoris). Three training sessions/week during 4 weeks	12 untrained health. Test (n = 6, 20.0 ± 0.8 years); Control (n = 6, 22 ± 0.6 years)	Random	24–48 h after last training session	10%	↑Strength 87%; ↑ MEP/Mmax amplitude 25%. ↓ SICI 35.4%	16
Hendy & Kidgell	2013	Metronome-paced resistance training of upper limb (wrist extensor). Three training sessions/week durng 3 weeks	20 untrained healthy. Test (n = 10, 25.7 ± 3.1 years, 5 M & 5 F); Control (n = 10, 24.4 ± 1.0 years, 7 M & 3 F)	Random	48–72 h after last training session	10%	↑ Strength 11.6%; ↑ MEP/Mmax amplitude 1.2%. ↓ CSP duration 9.9 ms. ↓ SICI 7.8%	18
Leung et al.	2013	Metronome-paced resistance training of upper limb (biceps brachii). Three training sessiones/week during 3 weeks	12 untrained healthy young. Test [1 M (23 years) & 5 F (24.6 ± 1.1 years)]; Control [2 M (33.0 ± 1.5 years) & 4 F (29.0 ± 6.2 years)]	Random	24–36 h after last training session	10%	↑ Strength 39%; ↑ MEP/Mmax amplitude 25.5%	17
Pearce et al	2013	Metronome-paced resistance training of upper limb (biceps brachii). Three training sessions/week during 3 weeks	18 untrained healthy. Test (n = 9, 25.3 ± 8.7 years, 4 M & 5 F); Control (n = 10, 23.8 ± 6.0 years, 5 M & 5 F)	Random	Within 48 h following last training session	10%	↑Strength 20.8%; ↑ MEP/Mmax amplitude 5.3%	19
Christie & Kamen	2014	Isometric resistance training of lower limb (tibial anterior). 3 training sessions/ week during 2 weeks	30 untrained healthy (21.9 ± 3.1 years. Test (n = 15); Control (n = 15)	Random	24–48 h after last training session	Rest	↑ Strength 17%; ↓ MEP/Mmax amplitude 1.4%; ↓ CSP duration 15 ms	18
Iglesias-Soler	2015	Self paced resistance training of lower limb (rectus femoris). 2 training sessions/ week during 5 weeks.	13 untrained healthy. n = 13. 22.5 ± 2.6 years. 7 M & 6 F.	Random	24–48 h after last training session	5%	↑ Strength 25%. No changes corticospinal parameters	18

(*continued on next page*)

Table 1 (*continued*)

Name	Year	Training	Subjects	Sampling	Post-training testing	% MVC at TMS	Results	D & B Score
Coombs et al	2016	Metrome-paced resistance training of upper limb (right wrist extensor and left wrist extensor). Three training sessions/week during 3 weeks	23 untrained healthy. Test RH (n = 8, 22.20 ± 2.06 years, 4 M & 4 F); Test LH (n = 8, 21.00 ± 2.21 years, 4 M & 4 F) Control (n = 7, 25.20 ± 2.71 years, 3 M & 4 F)	Random	24–36 h after last training session	5%	RH (↑ Strength 22%; ↑ MEP/Mmax amplitude 7.75%; ↓ CSP duration 4.5 ms; ↑ SICI 1.3%). LH (↑ Strength 18%;↑ MEP/Mmax amplitude 5.5%; ↓ CSP duration 10.4 ms; ↓ SICI 3.1%).	19
Manca et al	2016	Isometric resistance training of upper limb (first dorsal interosseuos). Three training sessions/week during 4 weeks	34 Untrained healthy young (25.5 ± 6.0 years, 23 M & 11 F)	Random	24 h after last training session	Rest	↑Strength 2.1%; ↑ MEP/Mmax amplitude 11%. No changes SICI.	23
Mason et al	2017	Metronome-paced resistance training of upper limb (biceps brachii). Three training sessions/week during 3 weeks	20 untrained healthy (18–35 years, 10 M & 10 W). Test (n = 10); Control (n = 10)	Random	Within 48 h following last training session	5%	↑Strength 29%; ↑ MEP/Mmax amplitude 10.1%. ↓ CSP duration 29.6 ms	19
Leung et al	2017	Metronome-paced & Self-paced resistance training of upper limb (biceps brachii). Three training sessiones/week during 4 weeks	33 untrained healthy (26.1 ± 6.8 years, 17 M & 16 F). Metronome-paced (n = 11); Self-paced (n = 11); Control (n = 11)	Random	Within 48 h following last training session	5%	Metronome-paced (↑ Strength 24%;↑ MEP/Mmax amplitude 8.1%; ↑ SICI 18.8%). Self-paced (↑ Strength 14%;↑ MEP/Mmax amplitude 0.64%; ↑ SICI 0.4%).	18
Siddique et al	2020	Metronome-paced, self-paced & isometric resistance training of upper limb (biceps brachii). Three training sessions/week for 4 weeks	42 untrained healthy (25.1 ± 5.8 years, 22 M & 20 F). Metronome-paced (n = 11); Self-paced (n = 11); Isometric (n = 10); Control (n = 10)	Random	Within 48 h following last training session	5%	Metronome-paced (↑ Strength 15.8%;↑ MEP/Mmax 52%;↑ SICI 18%). Self-paced (↑ Strength 17.8%;↓ MEP/Mmax 32.12%;↑ SICI 0.4%). Isometric (↑ Strength 5%;↑ MEP/Mmax 16.5%; ↑ SICI 3.3%).	18

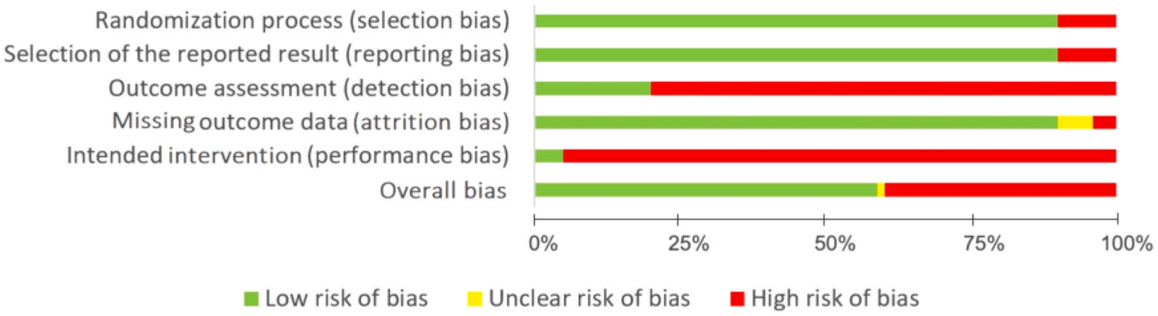

Fig. 2. Judgment of risk of bias expressed as a percentage of all included studies. The structure adopted the following order: (1) bias arising from the randomization process; (2) bias in selection of the reported result; (3) bias in measurement of the outcome; (4) bias due to missing outcome data, and (5) bias due to deviations from intended interventions.

condition of MEPs (active vs. resting muscles) as a moderating variable and compared the explanatory power of this model versus the model without moderation. The LR statistic for this model comparison was $\Delta\chi^2(\text{df} = 2) = 3.04$, $p < .210$. Therefore, we cannot conclude that there is a moderating effect of this variable.

3.2.2. *Changes in cortical silent period and muscle strength*

A multivariate meta-analysis was performed in studies that reported changes in CSP (SMD_{CSP}) and strength after RT estimated pooled effect sizes (95% CIs) for $\text{SMD}_{\text{CSP}} = -1.81$ (-2.80, -0.83), $SE = 0.50$, $p < .001$ and for $\text{SMD}_{\text{strength}} = 1.45$ (0.75, 2.14), $SE = 0.35$, $p < .001$. These results show that RT increased strength and reduced CSP in the analyzed studies. The homogeneity test for the model was statistically significant with Q (df = 43) = 105.12, $p < .001$, showing high heterogeneity across studies for both measures (I^2 for $\text{SMD}_{\text{CSP}} = .89$, for $\text{SMD}_{\text{strength}} = 0.79$). A negative correlation of – 0.62 between the population effect sizes was observed. The pooled effect sizes, individual effect sizes, and their 95% confidence ellipse are displayed in Fig. 4. Sensitivity analysis by varying the level of correlation between pre-test and post-test measures did not show substantial change in the reported estimates (data not shown). The LR test showed that both effect sizes were significant ($\Delta\chi^2$ (df = 2) = 10.22, $p = .006$).

3.2.3. *Changes in short-interval intracortical inhibition and muscle strength*

Multivariate meta-analyses on studies of changes in SICI and strength after RT show a significant increase in strength ($\text{SMD}_{\text{strength}} = 1.01$ (0.50, 1.51), $SE = 0.26$, $p < .001$) in the absence of significant changes in SICI ($\text{SMD}_{\text{SICI}} = 0.63$ (-1.24, 2.50), $SE = 0.95$, $p = .509$). Given that this lack of effect on the TMS variable could be conditioned by including studies in which SICI was measured at rest (Siddique et al., 2020b), we repeated this analysis including only studies measuring SICI during voluntary contraction. After applying this filter and excluding the effect sizes of the study by (Manca et al., 2016), the pooled effect sizes for both variables increased ($\text{SMD}_{\text{strength}} = 1.14$, $SE = 0.25$; $\text{SMD}_{\text{SICI}} = 0.77$, $SE = 1.05$), although the one corresponding to changes in SICI did not reach statistical significance ($p = .468$). The model showed significant

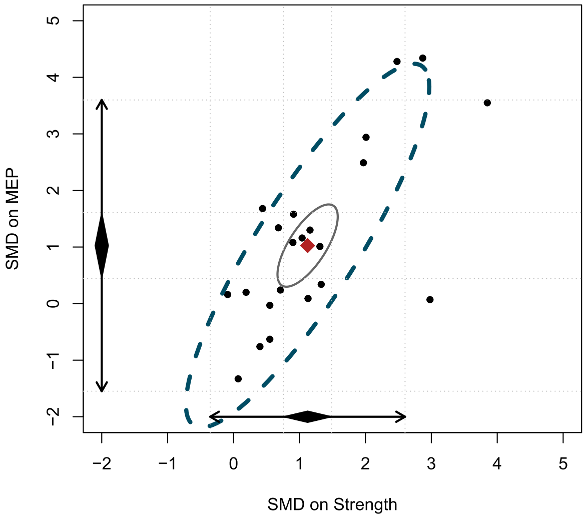

Fig. 3. Estimated effect sizes for changes in MEP amplitude and strength after RT and their 95% confidence ellipses. The red diamond in the center represents the estimated population effect sizes under a random-effects model. The solid ellipse (closest to the center) and the thick blue dashed line around the estimated population effect size represent its 95% confidence ellipse and the 95% confidence ellipse of the random effects, respectively. Note that the confidence ellipse for the random effects is quite large, indicating a high degree of heterogeneity. Most studies (individual black dots) are located within this confidence ellipse. The diamonds on the horizontal and vertical axes represent the estimated effect sizes and their 95% confidence intervals. Arrows in the horizontal and vertical axes represent the 95% confidence intervals of the random effects.

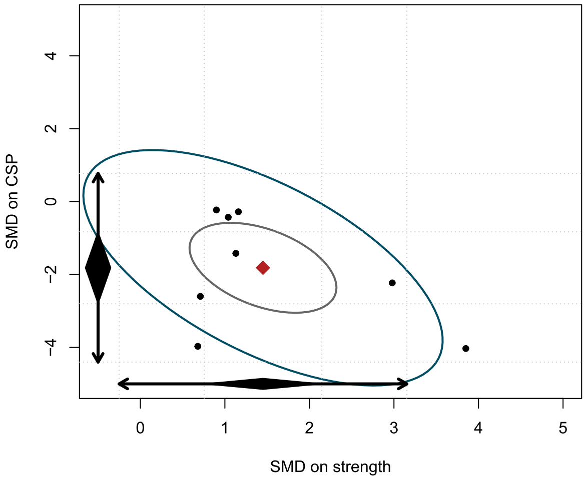

Fig. 4. Estimated effect sizes for changes in CSP duration and strength after RT and their 95% confidence ellipses.

heterogeneity with $Q(\text{df} = 20) = 116.13$, $p < .001$, showing high heterogeneity across studies for both measures (I^2 for $\text{SMD}_{\text{SICI}} = 0.96$, for $\text{SMD}_{\text{strength}} = 0.68$). The estimated correlation between the random effects was − 0.04, which was extremely low. Pooled effect sizes, individual effect sizes, and their 95% confidence ellipse are shown in Fig. 5. Sensitivity analysis by varying the level of correlation between pretest and post-test measures showed no substantial change in the reported estimates (data not shown).

3.2.4. Regression between corticospinal excitability and muscle strength

We then regressed the true effect size of strength change to the true effect size of the MEP amplitude change using the SEM-based meta-analysis approach. The estimated regression coefficient from the true

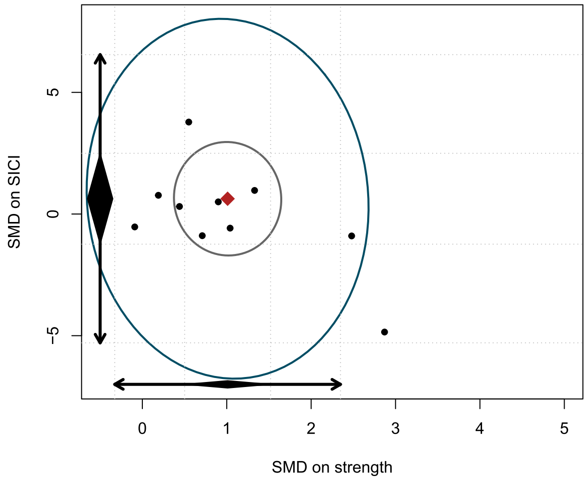

Fig. 5. Estimated effect sizes for changes in SICI and strength after RT and their 95% confidence ellipses.

effect size of the MEP amplitude change to the true effect size of strength change was.51, $SE = 0.12$, $z = 4.41$, and $p < .001$. The estimated R^2 and its 95% likelihood-based confidence interval (LBCI) were.77 (0.32,0.99). This indicates that the change in MEP amplitude after RT is quite strong in predicting the change in muscle strength.

3.2.5. Regression between the cortical silent period and muscle strength

The estimated regression coefficient from the true effect size of the change in CSP duration to the true effect size of change in strength was − 0.41, $SE = 0.19$, $z = -1.40$, and $p = .16$. The estimated R^2 and its 95% LBCI were.37 (0.00,0.99). This indicates that the change in the duration of the CSP is not a good predictor of the changes in strength after RT.

3.2.6. Regression between SICI and muscle strength

The estimated regression coefficient from the true effect size of the change in SICI to the true effect size of the strength change was − 0.01, $SE = 0.09$, $z = -0.12$, and $p = .90$. The estimated R^2 and its 95% LBCI were.01 (0.00,0.49). This indicates that the change in SICI is a poor predictor of the changes in strength after RT.

3.2.7. Moderation effects of training-related variables

To further explore the sources of the high heterogeneity among the studies included in our meta-analysis, we tested mixed-effect models within the multivariate SEM approach to assess the impact of two training-related variables on the TMS and strength results. Tables 2, 3 and 4 show the principal results of these analyses. The variation between effect sizes was significantly explained by exercise modality in the multivariate model for MEP and strength (LR statistics $\Delta\chi^2$ (df = 4) = 18.00, $p = .001$). The inclusion of this variable in the model explained 18.1% of the heterogeneity variability present in the multivariate analysis. Of the three exercise modalities studied, only MP training was associated with a post-training increase in both MEP amplitude ($\text{SMD}_{\text{MEP}} = 1.77$) and muscle strength ($\text{SMD}_{\text{strength}} = 1.66$) (Table 2). This exercise modality also showed the greatest effects on both MEP amplitude and strength following RT. A pooled negative effect of SP training on MEP amplitude was found, but this was not significant ($p = .280$). This exercise was associated at the trend level with increases in muscle strength ($p = .070$). In contrast, IM training was associated with a pooled positive ES in muscle strength ($p = .040$) but not with MEP amplitude ($p = .150$).

Training in the upper and lower extremities produced significant increases in MEP amplitude and strength following RT (Tables 2 and 3). The pooled effect sizes were larger in studies focused on the lower extremities. However, the 95% CI associated with the pooled effect size of lower limb training largely overlaps with that estimated for upper limb

Table 2
Summary statistics of the moderator analysis on MEP amplitude and muscle strength.

	MEP amplitude					Strength				
	k	*Pooled ES*	*95% CI*	*Q*[a]	*p*	*k*	*Pooled ES*	*95% CI*	*Q*[a]	*p*
Overall	23	1.03	0.44, 1.61			23	1.12	0.76, 1.49		
Trained vs. Untrained										
Training-related moderators										
Exercise modality	23			26.22	0.001	23			13.26	< 0.0001
Isometric	6	0.63	-0.22, 1.49			6	0.56 *	0.00, 1.25		
Self-paced	6	-0.48	-1.35,0.39			6	0.55	-0.04, 1.13		
Metronome-paced	11	1.77***	1.16, 2.39			11	1.66***	1.23, 2.09		
Limbs trained	23			3.06	0.08	23			0.025	0.87
Upper	17	0.68*	.05, 1.30			17	0.78***	.42, 1.13		
Lower	6	2.05***	.97, 3.13			6	2.09***	1.45, 2.73		

[a] *Q* for comparisons of the moderator subtypes.

* $p < .05$

*** $p < .001$

Table 3
Summary statistics of the moderator analysis on CSP duration and muscle strength.

	CSP duration					Strength				
	k	*Pooled ES*	*95% CI*	*Q*[a]	*p*	*k*	*Pooled ES*	*95% CI*	*Q*[a]	*p*
Overall	8	-1.81	-2.80, − 0.83			8	1.45	0.75, 2.14		
Trained vs. Untrained										
Training-related moderators										
Exercise modality	8			0.580	0.446	8			0.96	0.326
Isometric	2	-2.38*	-4.36, − 0.40			2	0.97	-0.28, 2.24		
Self-paced	NA					NA				
Metronome-paced	6	-1.62**	-2.73, − 0.50			6	1.65***	.85, 2.44		
Limbs trained	8			1.27	0.260	8			6.21	0.012
Upper	5	-1.35*	-2.48, − 0.21			5	0.88***	.29, 1.48		
Lower	3	-2.61***	-4.04, − 1.17			3	2.32***	1.41, 3.23		

[a] *Q* for comparisons of the moderator subtypes.

* $p < .05$

** $p < .01$

*** $p < .001$

Table 4
Summary statistics of the moderator analysis on SICI and muscle strength.

	SICI					Strength				
	k	*Pooled ES*	*95% CI*	*Q*[a]	*p*	*k*	*Pooled ES*	*95% CI*	*Q*[a]	*p*
Overall	11	0.62	-1.23, 2.49			11	1.01	0.50, 1.52		
Trained vs. Untrained										
Training-related moderators										
Exercise modality	11			0.12	0.733	11			1.52	0.217
Isometric	2	0.10	-4.12, 4.33			2	0.00	-0.62,0.62		
Self-paced	2	0.64	-3.59, 4.88			2	0.91*	.11, 1.70		
Metronome-paced	7	0.77	-1.59, 3.13			7	1.31***	.82, 1.79		
Limbs trained	11			7.73	0.005	11			9.73	0.002
Upper	9	1.33	-0.43, 3.10			9	0.70***	.29, 1.11		
Lower	2	-2.71	-6.43, 1.01			2	2.62***	.56, 1.52		

* $^{*}p < .01$

[a] *Q* for comparisons of the moderator subtypes.

* $p < .05$

*** $p < .001$

training. These results suggest that the increase in corticospinal excitability and strength associated with RT does not depend on the limbs used for training.

We then tested in the multivariate model for CSP and strength whether the exercise modality variable was able to explain part of the found heterogeneity. The results of this analysis are shown in Table 3. As can be seen, exercise modality could not explain the heterogeneity in the estimated effect sizes for changes in strength or changes in CSP duration (LR statistics $\Delta\chi^2$ (df = 2) = 2.62, p = .272). There was no representation of studies with SP RT in this analysis. In contrast, the trained limb (upper vs. lower limb) significantly explained the variability in the multivariate model that included changes in the duration of the CSP and changes in strength after RT (LR statistics $\Delta\chi^2$ (df = 2) = 6.37, p = .041). The inclusion of this variable in the model explained 8% of the heterogeneity variability present in the multivariate analysis. The pooled effect sizes were larger in studies focused on the lower extremities. However, the 95% CI associated with the pooled effect size of lower limb training largely overlaps with that estimated for upper limb training. These results suggest that the decrease in CSP and the increase in strength associated with RT do depend on the limbs used for training.

The exercise modality did not significantly explain the variability in the multivariate models of SICI and strength (LR statistics $\Delta\chi^2$ (df = 4) = 6.80, $p = .147$) (Table 4). On the contrary, the trained limb was a variable that significantly explained the heterogeneity among the reported effects (LR statistics $\Delta\chi^2$ (df = 2) = 16.30, $p < .001$). The inclusion of this variable in the model explained 9% of the heterogeneity variability present in the multivariate analysis. *Post hoc* comparison between upper vs lower limb RT showed that this moderation was mainly driven by differences in strength changes rather than by differences in SICI. The pooled effect sizes for strength were larger for lower limb training, although the 95% CIs overlapped to a large extent. Therefore, this analysis also suggests that the effect of RT on strength was not dependent on the trained limb.

3.2.8. Moderation effect of exercise modality on the corticospinal excitability-strength relationship

Additionally, we explored whether the relationship detected between corticospinal excitability and strength depended on the exercise modality used in RT. We fit three separate regression models, one for each exercise modality, again using the SEM-based meta-analysis approach. The estimated parameters and results of these analyses are summarized in Table 4. The change in muscle strength could be predicted by the change in MEP amplitude after MP RT training, while this relationship was not significant for the other two exercise modalities.

4. Discussion

This updated meta-analysis revealed that RT increases both muscle strength and corticospinal excitability. Results also showed a reduction of corticospinal inhibition, corroborating the findings of previous meta-analyses (Kidgell et al., 2017; Siddique et al., 2020b). To our knowledge, this is the first multivariate meta-analysis on neural adaptations to RT that studies the moderating effect of different training modalities in a differentiated manner (MP, SP, and IM). Training modality was identified as a major moderator of the relationship between corticospinal excitability and muscle strength, a finding that not only partially explains the heterogeneity of the ES reported on changes in corticospinal excitability and muscle strength after RT, but also mediates the relationship between these two variables.

4.1. Corticospinal excitability

Recent meta-analyses have described an increase in corticospinal excitability following RT. Kidgell et al. (2017) found that MEP increased slightly after RT but was not significant (SMD =0.27). In contrast, Siddique et al. (2020b) observed greater pooled effect sizes following RT (SMD =0.55), indicating a greater increase in corticospinal excitability. These variations in ES are likely due to differences in the ES calculations. In our meta-analysis, a higher ES of RT was found in the MEP amplitude (SMD = 1.03) following RT and compared to the control group, suggesting that RT modulates both cortical and spinal mechanisms. However, we observed a high heterogeneity influencing this analysis. This heterogeneity was partially explained after dividing the analysis of MEP amplitude into three common types of RT exercise. Here, we observed a much greater pooled effect size after MP compared to SP and IM RT. In fact, only MP RT yielded significant results vs. SP and IM.

There is a paucity of studies that directly compare the effect on corticospinal excitability of different types of training. This has prevented us from using meta-analytic techniques that directly compare these effects (e.g., network meta-analysis). An example of such comparative studies was carried out by Leung et al. (2017), which analyzed differences between MP and SP RT, finding a greater increase in MEP amplitude (8% vs. baseline) after MP RT vs. the null increase in MEP amplitude after SP RT (0.6%). The most recent study analyzed the differences between MP, SP and IM (Siddique et al., 2020a), observing a 52% increase in corticospinal excitability for MP and 18% for SP. However, IM training reduced corticospinal excitability by 32% compared to baseline.

These findings can potentially be attributed to variations in the engagement of the eccentric phase across the three analyzed RT protocols. It is worth highlighting that, unlike the SP or IM RT, the studies incorporating MP RT in this meta-analysis allocate over fifty percent of the movement emphasis towards the eccentric component. Consequently, when compared to the other two training modalities, MP RT places a greater emphasis on the eccentric phase of motion (Siddique et al., 2020a). Studies utilizing TMS have provided valuable insights into the distinct neural mechanisms involved in eccentric muscle contractions when compared to other types of muscle contractions. Although evidence is still limited, different neurophysiological studies have shown that eccentric contractions cause greater corticospinal excitability compared to concentric and isometric contractions (Abbruzzese et al., 1994; Gruber et al., 2009; Lepley et al., 2017). It is important to acknowledge, however, that the excitability measurements in these studies were conducted during a single bout of exercise, where participants performed various types of contractions. Therefore, caution should be exercised when interpreting the relationship between these findings and those observed in our meta-analysis.

MP RT over several weeks could lead to long-lasting increases in corticospinal excitability through known neuroplastic potentiation mechanisms (Voss et al., 2013). However, the role of this increase associated with MP RT is not fully clear. One possible explanation is that neurons in the motor cortex would increase the corticospinal drive to the muscle during eccentric exercise as a compensatory strategy to overcome the inhibition that occurs at the level of the muscle spindle (Abbruzzese et al., 1994; Gruber et al., 2009; Lepley et al., 2017). In other words, the muscle spindle, which would normally cause a reflex contraction of the muscle during lengthening, must be inhibited to allow eccentric contraction to occur, thereby increasing the cortical drive to the muscle (Duchateau and Enoka, 2016; Lepley et al., 2017). As others have suggested, MP RT training would increase sensory feedback during the eccentric phase, leading to facilitatory neurophysiological changes at the central level (Hortobágyi et al., 1997; Kidgell et al., 2015; Lepley et al., 2017).

MP RT would not only involve changes in the neural recruitment pattern and activation of neuroplastic processes at the level of the sensorimotor cortex involved in the trained muscle, but this type of training would also promote changes in brain regions not directly involved in the control of the trained muscle (Perrey, 2018). In relation to the contralateral primary motor area (to the active muscle), in cross-education studies it has been found that excitability can be modulated in intracortical circuits and corticospinal inhibition mechanisms of the ipsilateral hemisphere to the trained muscle (Coombs et al., 2016; Kidgell et al., 2015), while this effect is not appreciable for concentric RTs. One possible interpretation of these findings is that eccentric training would reduce interhemispheric inhibitory mechanisms in order to facilitate neural drive to trained muscles. However, there are few chronic cross-education studies evaluating this hypothesis (Manca et al., 2016).

Another possible explanation for why MP RT induces a greater increase in corticospinal excitability may be the fact that this type of motion involves the activation of specific areas of the brain such as the premotor cortex and supplementary motor area (Gerloff et al., 1998; Plow and Carey, 2012; Ackerley et al., 2011; Thaut et al., 2002). On the other hand, SP RT induces broader regions of activation within the cortical and subcortical areas of the brain (Leung et al., 2017). Therefore, the repeated activation of cortical areas observed in MP RT may be important for the induction of use-dependent plasticity (Pascual-Leone et al., 1995; Sanes and Donoghue, 2000; Yue and Cole, 1992). These results support our hypothesis that MP RT increases corticospinal excitability more than other types of exercise.

4.2. *Corticospinal inhibition*

This work showed a general reduction in corticospinal inhibition after several weeks of RT, which was also observed in previous meta-analyses (Kidgell et al., 2017; Siddique et al., 2020b). We found a clear reduction in CSP after 2–4 weeks of RT was performed in the 8 included studies ($SMD_{CSP} = -1.81$). Concomitant with this shortening of the duration of CSP, our analysis revealed an increase in strength after RT ($SMD_{strength} = 1.45$), but changes in CSP were not good predictors of changes in strength. CSP is primarily initiated at the M1 level and is mediated by $GABA_B$, indicating a brief interruption of the neural drive to the neuromuscular junction (Yacyshyn et al., 2016). However, various sources of evidence suggest that CSP is not a purely cortical phenomenon. CSP would have an early part (first 50–75 ms) that originates at the spinal level, and which would be reflected by a profound depression of the H-reflex (Fuhr et al., 1991), and that it would be a consequence of the activation of known mechanisms such as recurrent inhibition by Renshaw cell activation, motoneuron after-hyperpolarization, or synaptic inhibition via Ia inhibitory interneurons (Chen et al., 2008). It seems that RT could reduce synaptic efficiency between the inhibitory Rensahw cell and the motor neuron pool, eventually increasing motor neuronal output (Siddique et al., 2020b). However, to date, there is no direct experimental evidence of a possible effect of RT on the cortical component (50–200 ms) of the CSP. An interesting approach would be to measure TMS-induced EEG changes after RT (Farzan et al., 2013). Another possible explanation for the lack of predictability of CSP on strength changes after RT may be due to methodological variability across studies when recording CSP (Siddique et al., 2020b), both in levels of sustained voluntary contraction and in suprathreshold intensities of the magnetic pulse (see Table 1).

A high degree of heterogeneity was found across CSP and strength effect sizes. However, the inclusion of exercise modalities in the multivariate model for CSP and strength did not explain this heterogeneity. Therefore, our data suggest that the effects of RT on the CSP-strength relationship are independent of the exercise modality. This result could be explained in part due to the lack of studies that analyze different exercise modalities (only 2 IM and 1 SP that met inclusion / exclusion criteria). Moreover, to date, no study has directly confronted the different exercise modalities analyzed in this study. Therefore, the conclusions of the analysis carried out with the moderating variables in CSP should be taken with caution and, there are still too few studies, especially using SP training, to reach robust conclusions.

Our multivariate analysis indicates that there was no significant decrease in SICI ($SMD_{SICI} = 0.63$), but there was a significant increase in strength ($SMD_{strength} = 1.01$) after RT. When we specifically looked at studies on SICI under voluntary activation, the results remained consistent, and there were no significant changes in the observed effects of RT on SICI and strength. Of the 12 studies that measured SICI in our meta-analysis, 7 performed MP RT, 3 SP RT, and 2 studies performed IM RT. SICI measured the intracortical inhibitory mechanism mediated by $GABA_A$, resulting in synaptic inhibition of corticospinal cells targeted by the conditioning stimulus (Chu et al., 2008; Kujirai et al., 1993). Thus, SICI enables the measurement of the inhibitory cortical mechanism. Our results suggest a trend of reduction of SICI, although the results were not significant. The lack of a significant effect of RT on the pooled effect size of SICI is in some discrepancy with previous meta-analyses performed from the univariate perspective, where a significant decrease in SICI is reported after 2–4 weeks (Kidgell et al., 2017; Siddique et al., 2020b). Among the variables that could explain the differences between our meta-analysis and previous ones, we included a larger number of effect sizes, as well as the use of different methods for the calculation of effect sizes or estimation of random-effects models.

In general, our meta-analysis shows that RT can selectively alter $GABA_B$- mediated intracortical motor inhibitory mechanisms, while $GABA_A$- mediated mechanisms are relatively unchanged. However, we cannot overlook the possible effects of RT on intraspinal inhibitory circuits that may affect the TMS measures.

4.3. *Muscle strength*

Our meta-analysis found an overall greater increase in strength (SMD = 1.12) after RT. This finding corroborates previous meta-analyses indicating that 2–4 weeks of regular RT increase final force production (Kidgell et al., 2017; Siddique et al., 2020b). Differences in the magnitude of the estimated effect sizes with respect to previous meta-analyses may be explained by the inclusion of a different number of studies (due to different inclusion criteria) and disparities in the effect size estimation methods.

In addition to the observed effects on MEP sizes, we observed that MP RT resulted in the most significant improvement in muscle strength upon completion of the training program, surpassing the effects of SP and IM RT. These disparities between RT types can be attributed to the amount of effort and emphasis placed on the eccentric phase of movement during weightlifting repetitions in MP RT. Specifically, in the MP RT studies included in our meta-analysis, the motion incorporates a 3-second concentric phase followed by a 4-second eccentric phase. In contrast, SP RT involved faster tempos (Siddique et al., 2020b), with individuals moving the weight without external pacing, primarily focusing on the concentric lifting phase and exerting minimal effort during the eccentric portion, simply releasing the load. An interesting systematic review and meta-analysis (Roig et al., 2009) comparing eccentric with concentric exercise revealed that training solely with eccentric contractions increased total strength significantly more than with isolated concentric exercises. Similar results were obtained in a more recent meta-analysis (Schoenfeld et al., 2017), where a greater gain in strength was found after eccentric exercise alone compared to concentric exercise.

The pooled effect sizes associated with each exercise modality estimated in the present meta-analysis are, to some extent, in discordance with those reported in individual studies that performed comparative analysis between modalities. For example, Siddique et al. (2020a) reported stronger strength gains after SP (25%) than MP (18%), although the effect size of the latter was larger (SP's $d = 2.33$ vs. MP's $d = 3.22$). In our study, the estimated size effects were.55 for SP and 1.66 for MP. This inconsistency may be a consequence of the fact that the studies reviewed have not reported comparative measures between the different training modalities. Therefore, more studies are needed comparing different exercise modalities within the same study to overcome this limitation.

4.4. *Relationship between MEP and strength*

Our multivariate SEM-based meta-analysis revealed that increased muscle strength is partially explained by increased corticospinal excitability and not only due to muscle hypertrophy, as some authors have suggested (Bodine et al., 2001; Damas et al., 2018, 2016; Schiaffino et al., 2013). It should be noted that only MP RT showed a significant relationship between the increase in MEP amplitude and muscle strength, which was not significant for SP or IM RT. Our results suggest that MP RT induces corticospinal changes and that up-regulation of corticospinal excitability due to RT is related to increased strength.

Although SP and IM RT increased strength, this increase could involve different neurophysiological mechanisms compared to MP RT. There is experimental evidence in primates associating SP and IM RT with neural adaptations in the intracortical and reticulospinal circuits, while corticospinal is not a dominant factor (Glover and Baker, 2020). Reticulospinal involvement in RT is a mechanism that deserves attention, but its accessibility in humans in a noninvasive manner is still under development (Atkinson et al., 2022). Regarding the possible involvement of inhibitory circuits, recent meta-analyses (Kidgell et al., 2017; Siddique et al., 2020b) proposed that strength training is characterized by changes in intracortical and corticospinal inhibitory networks (such as the role of Renshaw cell), rather than corticospinal excitability. However, the relationship between training modalities and inhibitory circuits could not be fully verified in our meta-analysis, probably influenced by the paucity of studies in SP and IM RT. Nevertheless, there is a trend toward a reduction of inhibitory phenomena associated with SP and IM RT, which would support this hypothesis. In addition, adaptations may also occur at the spinal level (Inghilleri et al., 1993; Siddique et al., 2020b), for example, at the motor neuron level, although there are technical limitations associated with these studies (Carroll et al., 2011).

This finding could be considered important to the rehabilitation of certain pathologies, such as post-stroke patients. In this pathology, prompt recovery of brain functionality is essential to return to normal activity, and many researchers focus their work on finding a way to rapidly restore lost brain connections (Alia et al., 2017). In this scenario, non-invasive brain stimulation techniques such as transcranial direct current stimulation or repetitive TMS may be useful to improve the plastic remodeling of areas of brain damage (Alia et al., 2017; Alisar et al., 2020; Bornheim et al., 2020a, 2020b). Increasing corticospinal excitability may benefit the recovery of these patients, and therefore MP RT could support, by combining with other rehabilitation therapies, a rapid recovery of this population.

5. Conclusions

This is the first systematic review and multivariate meta-analysis to provide quantitative results of how corticospinal excitability/inhibition and muscle strength are modulated simultaneously following RT. It also quantifies how corticospinal excitability/inhibition and muscle strength are affected by three common exercise modalities: MP, SP, and IM RT. Overall, we found that improvement in muscle strength following RT is accompanied by a significant increase in the amplitude of the MEP, a significant decrease on CSP and non-significant effect in SICI, suggesting that the gain in strength may not only be due to muscle hypertrophy and that neural adaptation may influence the final increase in force. We also demonstrated that MP RT generated the greatest increase in corticospinal excitability and muscle strength compared to SP and IM exercise. In fact, a significant relationship between corticospinal excitability and strength was only observed after MP RT.

CRediT authorship contribution statement

JG-F. design, data collection, analysis, writing; JFM-R. design, data collection, analysis, writing; PM design, analysis, writing.

Competing interest

The authors declare no competing interest.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105289.

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