Determining the early corticospinal-motoneuronal responses to strength training : A systematic review and meta-analysis

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Abstract: Several studies have used transcranial magnetic stimulation to probe the corticospinal-motoneuronal responses to a single session of strength training; however, the findings are inconsistent. This systematic review and meta-analysis examined whether a single bout of strength training affects the excitability and inhibition of intracortical circuits of the primary motor cortex (M1) and the corticospinal-motoneuronal pathway. A systematic review was completed, tracking studies between January 1990 and May 2018. The methodological quality of studies was determined using the Downs and Black quality index. Data were synthesised and interpreted from meta-analysis. Nine studies (n = 107) investigating the acute corticospinal-motoneuronal responses to strength training met the inclusion criteria. Meta-analyses detected that after strength training compared to control, corticospinal excitability [standardised mean difference (SMD), 1.26; 95% confidence interval (CI), 0.88, 1.63; $p < 0.0001$] and intracortical facilitation (ICF) (SMD, 1.60; 95% CI, 0.18, 3.02; $p = 0.003$) were increased. The duration of the corticospinal silent period was reduced (SMD, –17.57; 95% CI, –21.12, –14.01; $p = 0.00001$), but strength training had no effect on the excitability of the intracortical inhibitory circuits [short-interval intracortical inhibition (SICI) SMD, 1.01; 95% CI, –1.67, 3.69; $p = 0.46$; long-interval intracortical inhibition (LICI) SMD, 0.50; 95% CI, –1.13, 2.13; $p = 0.55$]. Strength training increased the excitability of corticospinal axons (SMD, 4.47; 95% CI, 3.45, 5.49; $p < 0.0001$). This systematic review and meta-analyses revealed that the acute neural changes to strength training involve subtle changes along the entire neuroaxis from the M1 to the spinal cord. These findings suggest that strength training is a clinically useful tool to modulate intracortical circuits involved in motor control.

Keywords: corticospinal; cortical facilitation; cortical inhibition; motor evoked potential; strength training.

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Introduction

It is well established that the human nervous system can modify its function in response to physical activity or experience (Kleim et al., 2002; Katiuscia et al., 2009; Kidgell et al., 2017). This response has been termed *plasticity* and involves reorganisation of neural circuits in the primary motor cortex (M1) that control movement (Sanes and Donoghue, 2000). Among many different ways, strength training has also been shown to influence plastic changes in the central nervous system (Hendy and Kidgell, 2013; Nuzzo et al., 2016; Frazer et al., 2017; Leung et al., 2017; Mason et al., 2017).

Strength training improves muscle strength, which can be broadly defined as the maximal force or torque that can be developed by the muscles performing a specific movement (Enoka, 1988). Studies have demonstrated that muscle strength can be improved after a single session of strength training (Selvanayagam et al., 2011; Hendy and Kidgell, 2014; Nuzzo et al., 2016; Latella et al., 2017). Suggestions for this acute development of muscle strength have been attributed to neurological factors (Carroll et al., 2002; Kidgell et al., 2017) Griffin and

Cafarelli, 2007; Kidgell et al., 2010; Christie and Kamen, 2013).

Transcranial magnetic stimulation (TMS) has emerged as the leading candidate to provide insight into the synaptic activity of the corticocortical circuitry of the M1 and of the corticospinal-motoneuronal pathway. TMS of the M1 induces muscle responses, recorded in the target muscle by surface electromyography (sEMG) and are termed *motor evoked potentials* (MEPs). Changes in the amplitude of MEPs have been examined to study the physiology of the corticospinal-motoneuronal pathway after strength training (Carroll et al., 2001). Typically, a variety of parameters of the MEP can be investigated, including MEP amplitude, motor threshold, corticospinal silent period duration, and facilitation of the intracortical circuits of the M1 (Carroll et al., 2002; Christie and Kamen, 2013; Hendy and Kidgell, 2013; Mason et al., 2017).

There are now many studies that have used TMS to investigate the integrity of the corticospinal-motoneuronal pathway after a single session of strength training (Selvanayagam et al., 2011; Hendy and Kidgell, 2014; Brandner et al., 2015; Leung et al., 2015; Latella et al., 2016, 2017, 2018; Nuzzo et al., 2016). For example, a single session of heavy-load elbow flexion strength training increased MEPs evoked by single-pulse TMS (Leung et al., 2015). More recently, Latella et al. (2017) reported increased MEP amplitude after a single session of both heavy-loaded and hypertrophy-based strength training. However, in contrast, Latella et al. (2016) and Selvanayagam et al. (2011) reported reduced MEP amplitude after a single session of strength training. Beyond measuring the excitability of the corticospinal-motoneuronal pathway with single-pulse TMS, paired-pulse TMS is also capable of assessing intracortical facilitation (ICF), which estimates cortical excitability evoked by a conditioning stimulus followed by a test stimulus. There is now preliminary evidence to suggest that a single bout of strength training affects the excitability of the intracortical circuitry of the M1 towards facilitation (Latella et al., 2016, 2017, 2018). However, the magnitude of facilitation varies across studies and the pooled effect remains unclear.

MEP responses to a single session of strength training likely arise from changes in synaptic efficacy along the corticospinal-motoneuronal pathway and in the intrinsic circuitry of the M1. However, TMS is limited in that it cannot identify the precise location of synaptic modification after an intervention; thus, stimulating the axons of corticospinal fibres assists to identify the level of synaptic modification. Cervicomedullary MEPs (CMEPs) are generated subcortically through electrical stimulation at the cervicomedullary junction. Electrical current passing through electrodes evokes a descending volley, which like TMS is quantified using sEMG (Nuzzo et al., 2016). Importantly, because cervicomedullary stimulation is delivered inferior to the level of the M1, it is regarded as a measure of spinal excitability (Taylor and Gandevia, 2004; Taylor, 2006). By comparing changes in CMEP and MEP amplitudes after strength training, it is possible to infer whether increases in excitability occur at a cortical or spinal level, or both. However, the overall effect of strength training on the excitability of corticospinal axons is not known.

Outside of changes in the excitability of the corticospinal-motoneuronal pathway, changes in corticospinal inhibition might also offer an important insight into the early neural responses to strength training. For example, evidence regarding changes in the duration of the corticospinal silent period, reflecting γ-aminobutryic acid B ($GABA_B$) receptor activity, after a single session of strength training is relatively limited, and there is no clear consensus (Ruotsalainen et al., 2014; Latella et al., 2017, 2018). A tentative explanation for the discrepancy between studies likely resides in the parameters of the strength training task, for example, the muscles trained, the TMS stimulus intensity used, the training load, and the type of strength training (paced, nonpaced, heavy-load, or hypertrophy-based training). Similar to the corticospinal silent period, some studies have assessed the effect of strength training using short-interval intracortical inhibition (SICI) with interstimulus intervals between 1 and 5 ms that targeted $GABA_A$-mediated inhibition (Brandner et al., 2015; Leung et al., 2015; Latella et al., 2016, 2017, 2018). There is now evidence that shows SICI is reduced after a single session of strength training (Hendy and Kidgell, 2014; Brandner et al., 2015; Leung et al., 2015; Latella et al., 2016, 2017, 2018); however, the overall consensus of these changes is not clear and warrants a systematic investigation to determine whether the effects are meaningful. Similarly, understanding the effect of a single session of strength training on long-interval intracortical inhibition (LICI), which is assessed using a longer inter-stimulus interval between 50 and 200 ms and is considered a measure of $GABA_B$-mediated cortical inhibition (Rogasch et al., 2014), requires further investigation. Only three studies have examined LICI after a single session of strength training (Latella et al., 2016, 2017, 2018), and there has only been one study that has examined the training-related effects of strength training on LICI (Manca et al., 2016). Thus, there is a need to determine the overall effect of strength training on these intracortical inhibitory circuits of the M1.

TMS is a valuable tool in assessing the corticospinal-motoneuronal responses to strength training, leading to growing interest and relevance to clinical and practical

applications. Although the corticospinal-motoneuronal responses to short-term, multisession strength training programs (Kidgell et al., 2017) and other forms of motor training (Dayan and Cohen, 2011; Manca et al., 2018) are now well established, no such consensus currently exists for the acute corticospinal-motoneuronal responses after a single session of strength training. It is currently unknown whether the acute neurological responses to a single session of strength training align with the longer-term adaptations seen across multiple training sessions (Kidgell et al., 2017) or whether an acute session of strength training elicits unique responses due to factors such as fatigue (Goodall et al., 2018). Determining these early neural responses has implications for the design and structure of strength training programs in a range of contexts, including motor rehabilitation, injury prevention and rehabilitation, and long-term athletic development. Consequently, the aim of this systematic review and meta-analysis was to examine whether a single session of strength training has an effect on the intracortical circuits of the M1 and the corticospinal-motoneuronal pathway. Critically, understanding the early neural responses is a necessary step towards understanding the longer-term responses to strength development in numerous clinical and healthy populations.

Method

Literature search strategy

A standardised search strategy (see Table 1) used the following electronic databases: PubMed/MEDLINE, Science Direct, SciVerse, SCOPUS, Sport Discus, and Web of Science were searched from January 1990 until the first week of May 2018. A search strategy was conducted combining 'strength training' and its synonyms ('resistance training,' 'weight training,' 'and resistive exercise') with 'neural adaptations' and 'neuronal plasticity' as keywords. The following key terms were searched in combination with the above terms: 'transcranial magnetic stimulation,' 'TMS,' 'paired-pulse,' 'motor cortex,' 'motor evoked potential,' 'short-interval intracortical inhibition,' 'intracortical facilitation,' 'cervicomedullary evoked potential,' and 'cortical silent period.'

Table 1: Search strategy examples used to yield the acute corticospinal-motoneuronal responses to strength training.

MEDLINE (Ovid)	Scopus
1. Resistance training (inc related terms)	1. (TS = resistance training) AND Language: (English) AND Document types: (Article). Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Time span = 1990–2016
2. Limit 1 to (English language and full text and humans and yr = '1990-current')	2. (TS = exercise) AND Language: (English) AND Document types: (Article). Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Time span = 1990–2016
3. Exercise (inc related terms)	3. (TS = strength training) AND Language: (English) AND Document types: (Article). Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Time span = 1990–2016
4. Limit 3 to (English language and full text and humans and yr = '1990-current')	4. #3 or #2 or #1. Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Time span = 1990–2016
5. Strength training (inc related terms)	5. (TS = transcranial magnetic stimulation) AND Language: (English) AND Document types: (Article). Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Time span = 1990–2016
6. Limit 5 to (English language and full text and humans and yr = '1990-current')	6. (TS = motor evoked potential*) AND Language: (English) AND Document types: (Article). Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Time span = 1990–2016
7. Transcranial magnetic stimulation (inc related terms)	7. (TS = cortical silent period) AND Language: (English) AND Document types: (Article). Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Time span = 1990–2016
8. Limit 7 to (English language and full text and humans and yr = '1990-current')	8. (TS = intracortical inhibition) AND Language: (English) AND Document types: (Article). Indexes = Sci-Expanded, ESCI, CCR-Expanded, IC Time span = 1990–2016
9. Motor evoked potential* (inc related terms)	9. #5 and #4
10. Cervicomedullary evoked potential*(inc related terms)	10. #6 and #4
11. Limit 9 to (English language and full text and humans and yr = '1990-current')	11. #7 and #4
12. Cortical silent period (inc related terms)	12. #8 and #4
13. Limit 11 to (English language and full text and humans and yr = '1990-current')	
14. Intracortical inhibition (inc related terms)	
15. Limit 13 to (English language and full text and humans and yr = '1990-current')	
16. #2 or #4 or #6	
17. #8 and #15	
18. #10 and #15	
19. #12 and #15	
20. #14 and #15	

Each database was searched from January 1990 to May 2018. References from previous published literature were additionally searched. Figure 2 outlines the flow of studies removed after the application of each criterion according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). Although commonly used to report on randomised trials, PRISMA has been used to systematically review quasi-experimental research (Downs and Black, 1998; Liberati et al., 2009).

Selection of studies

The initial search was undertaken by two of the authors (JM and DJK). All titles and corresponding abstracts were retrieved and then screened. Any items that were outside the purposes of the present meta-analysis were removed. After screening of titles and abstracts, two authors (AKF and AJP) independently selected all included articles. At this point, all duplicated studies were removed. Any full-text article that potentially satisfied the inclusion criteria was carefully read, and eligible studies were then identified and included in the meta-analysis. In the case of disagreement, both assessors reviewed each study independently, and a third assessor (AMG) graded any discrepancies.

Eligibility criteria – exclusion and inclusion

Studies were considered for review if they met the following criteria: (1) recreationally trained and untrained healthy young adults of either sex between the ages of 18 and 40 years; (2) training intervention restricted to one single session of strength or resistance training; (3) strength training involved a training load that was greater than 50% of the maximal load; (4) studies must have compared an intervention to a control condition; (5) stimulation of M1 within 1 h of the cessation of training to quantify changes in excitability and inhibition through single-pulse measures such as MEPs (recorded in both active and resting muscles) and CMEPs as well as paired-pulse measures such as SICI, LICI, and ICF. Exclusion criteria established included diseased populations, non-English publications, non-peer-reviewed proceedings and theses, as well as studies that used nontypical strength training techniques such as superimposed electrical stimulation of the muscle or transcranial direct current stimulation during training. Studies were also excluded if there was no comparison to a control group.

Quality assessment and risk of bias

Two reviewers (AG and DJK) used a modified version of the Downs and Black (1998) checklist (Table 2) to assess the quality of included studies. A higher summed score, taking into account factors such as blinding of participants and researchers and validity of methods and analysis, indicates superior quality of study, thereby increasing validity of conclusions. Furthermore, the Cochrane Risk of Bias tool (Higgins et al., 2011) for randomised controlled trials rates trial quality on six domains: sequence allocation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias (Table 3). A rating of 'low' or 'high' was assigned if criteria for a low or high risk of bias were met, respectively. The risk of bias was judged 'unclear' if inadequate details for the criterion were reported.

Data extraction and analyses

For all included articles, data extraction involved the retrieval of study characteristics (author, year, sample size, and study design), participant demographic (age, sex), and strength training protocol (isometric, dynamic, upper body, lower body). In addition, the following outcome measures from each study were extracted from the available text: MEP amplitude (peak-to-peak waveform and expressed either as a raw amplitude or a percentage of peripheral M-wave amplitude); cortical silent period, quantified as the duration from the onset of MEP waveform to the return of uninterrupted sEMG activity (Wilson et al., 1993); and CMEPs (Taylor, 2006). Paired-pulse measures in the meta-analysis were SICI, LICI, and ICF, which were quantified as the ratio of the test stimulus and conditioning stimulus (Kujirai et al., 1993). Where the reported data were not sufficient for the purposes of this review, the corresponding author of the study was contacted and relevant data were requested. Where mean ± SD or SE values were not provided for postintervention parameters, the data were extracted from the graphs with Plot Digitizer software (Joseph, 2011). Plot Digitizer is a program for extracting data presented in papers as linear, logarithmic axis scales and scatter plots. After calibration of the image, data values are extracted by clicking on the data points.

Statistical analysis

The post-strength training data from the experimental and control groups were used from each study for

Table 2: Characteristics of included studies with the Downs and Black quality checklist.

Study	Country	Design	Evidence level	Training	Sample size	Participant characteristics	Age mean ± SD (years)	Sampling	Key DV	Key measure(s)	Results	Score
Hendy and Kidgell (2014)	Australia	Pretest–posttest crossover	III-1	Four sets, 6–8 reps at 70% 1-RM	10	Untrained healthy young	26 ± 1	Random	Corticospinal excitability and inhibition	MEP amplitude, SICI ratio	↑ MEP amplitude 2%, ↓ SICI 1.6%	22
Latella et al. (2016)	Australia	Pretest–posttest crossover	III-1	Five sets, three reps at 94% 1-RM	14	Previous training history, healthy young	26 ± 5	Random	Corticospinal excitability, ICF, LICI	MEP amplitude, ratio, ICF ratio, LICI ratio	↓ MEP amplitude 44%, ↑ICF 36%, ↑ LICI 33%	20
Latella et al. (2017) (hypertrophy)	Australia	Pretest–posttest crossover	III-1	Three sets, 12 reps at 67% 1-RM	14	Previous training history, healthy young	26 ± 5	Random	Corticospinal excitability and inhibition, ICF, LICI	MEP amplitude, cSP duration, SICI ratio, LICI ratio, ICF ratio	↑ MEP amplitude 77%, ↓ cSP duration 18%, ↑ ICF 83%, ↓ SICI 123%, ↑ LICI 8%	20
Leung et al. (2015) (self-paced)	Australia	Controlled pretest–posttest	III-1	Four sets, 6–8 reps at 70%–80% 1-RM	11	Untrained healthy young	26 ± 7	Random	Corticospinal excitability, intracortical inhibition	MEP amplitude, SICI ratio	↑ MEP amplitude 19%, ↑ SICI 6%	18
Leung et al. (2015) (metronome-paced)	Australia	Controlled pretest–posttest	III-1	Four sets, 6–8 reps at 70%–80% 1-RM	11	Untrained healthy young	26 ± 7	Random	Corticospinal excitability, intracortical inhibition	MEP amplitude, SICI ratio	↑ MEP amplitude 43%, ↓ SICI 19%	18
Nuzzo et al. (2016) (ballistic concentric)	Australia	Pretest–posttest crossover	III-1	12 sets, eight maximal isometric reps	10	Healthy young, training status unreported	24 ± 6	Random	Corticospinal excitability, cervicomedullary excitability	MEP amplitude, CMEP	↑ MEP area 330%, ↑CMEP area 49%	19
Nuzzo et al. (2016) (ballistic isometric)	Australia	Pretest–posttest crossover	III-1	12 sets, eight maximal isometric reps	14	Untrained healthy young	24 ± 5	Random	Cervicomedullary excitability, corticospinal excitability	CMEP area, MEP area	↑ CMEP amplitude 42%, ↑ MEP 268%	19
Nuzzo et al. (2016) (slow ramped isomeric)	Australia	Pretest–posttest crossover	III-1	12 sets, eight maximal isometric reps	14	Untrained healthy young	24 ± 5	Random	Cervicomedullary excitability, corticospinal excitability	CMEP amplitude	↑CMEP amplitude 32%, ↑ MEP area 217%	19

Table 3: Cochrane risk of bias.

Study/study subgroup	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other potential bias
Hendy and Kidgell (2014)	–	+	–	+	–	–	Same lab group as two other subgroups
Latella et al. (2016)	–	+	+	+	–	–	Same lab group as two other subgroups
Latella et al. (2017) (strength)	–	+	+	+	–	–	Same lab group as two other subgroups
Latella et al. (2017) (hypertrophy)	–	+	+	+	–	–	Same lab group as two other subgroups
Leung et al. (2015) (metronome paced)	–	+	+	+	–	–	Same lab group as two other subgroups
Leung et al. (2015) (self-paced)	–	+	+	+	–	–	Same lab group as two other subgroups
Nuzzo et al. (2016) (ballistic isometric)	–	+	+	+	–	–	Same lab group as one other subgroup
Nuzzo et al. (2016) (ballistic concentric)	–	+	+	+	–	–	Same lab group as one other subgroup
Nuzzo et al. (2016) (slow ramped)	–	+	+	+	–	–	Same lab group as one other subgroup

+, High risk of bias; –, low risk of bias.
Criteria established from the Cochran Collaboration tool for assessing risk of bias.

the following variables: MEP excitability, corticospinal silent period duration, CMEP, SICI, LICI, and ICF. As systematic influences and random error were predicted to be present between study-level effect sizes, a random-effects meta-analysis was performed to compare the overall pooled standardised mean differences (SMDs) for the main outcome measures (Borenstein et al., 2010). SMDs with 95% confidence intervals (CIs) were used to measure the intervention effect as the included studies presented outcome measures in a variety of ways. Using SMDs allowed the results of the studies to be combined on a uniform scale whilst also expressing the size of the intervention effect in each study relative to the variability observed in that study (SMD = difference in mean outcome between group/standard deviation of outcome among participants). The SMD values of $0.20 \leq 0.49$ indicate small, $0.50 \leq 0.79$ indicate medium, and ≥ 0.80 indicate large effects (Cohen, 1988). Heterogeneity was measured using the I^2 statistic, which indicates the percentage variance between studies with cutoff points corresponding to low (25%), moderate (50%), and high (75%) heterogeneity. Funnel plots assessed publication bias; however, because of the small number of included studies, plots were not analysed with Egger's regression test but were inspected visually. All statistical analyses were performed in RevMan 5.3 (Review Manager, The Cochrane Collaboration) using an α level of $p < 0.05$ to determine significance.

Results

Figure 1 outlines the PRISMA flow chart showing the process of study identification, screening, and evaluation of the eligibility of included studies. The initial search identified 829 titles and abstracts; the removal of 290 duplicates narrowed the field to 539 potential entries. After screening against the exclusion criteria, 435 papers were removed, leaving 104 papers to be assessed for eligibility. As outlined in Figure 1, a further 73 of these were removed for a range of reasons, including analysis of multiple sessions instead of a single session or the use of nonconventional strength training methods such as vibration training and fatiguing exercise. After an additional search brought up one record, 32 articles were included for analysis. Of these, 23 were removed (reasons outlined in Figure 1), leaving nine records for the final inclusion.

Quality assessment

Table 2 contains the quality assessment of each included study, according to the Downs and Black checklist. The Downs and Black checklist revealed that studies meeting the inclusion criteria ranged between 18 and 22 points (out of a possible 32 points), with a mean score of 19.3 ± 1.3

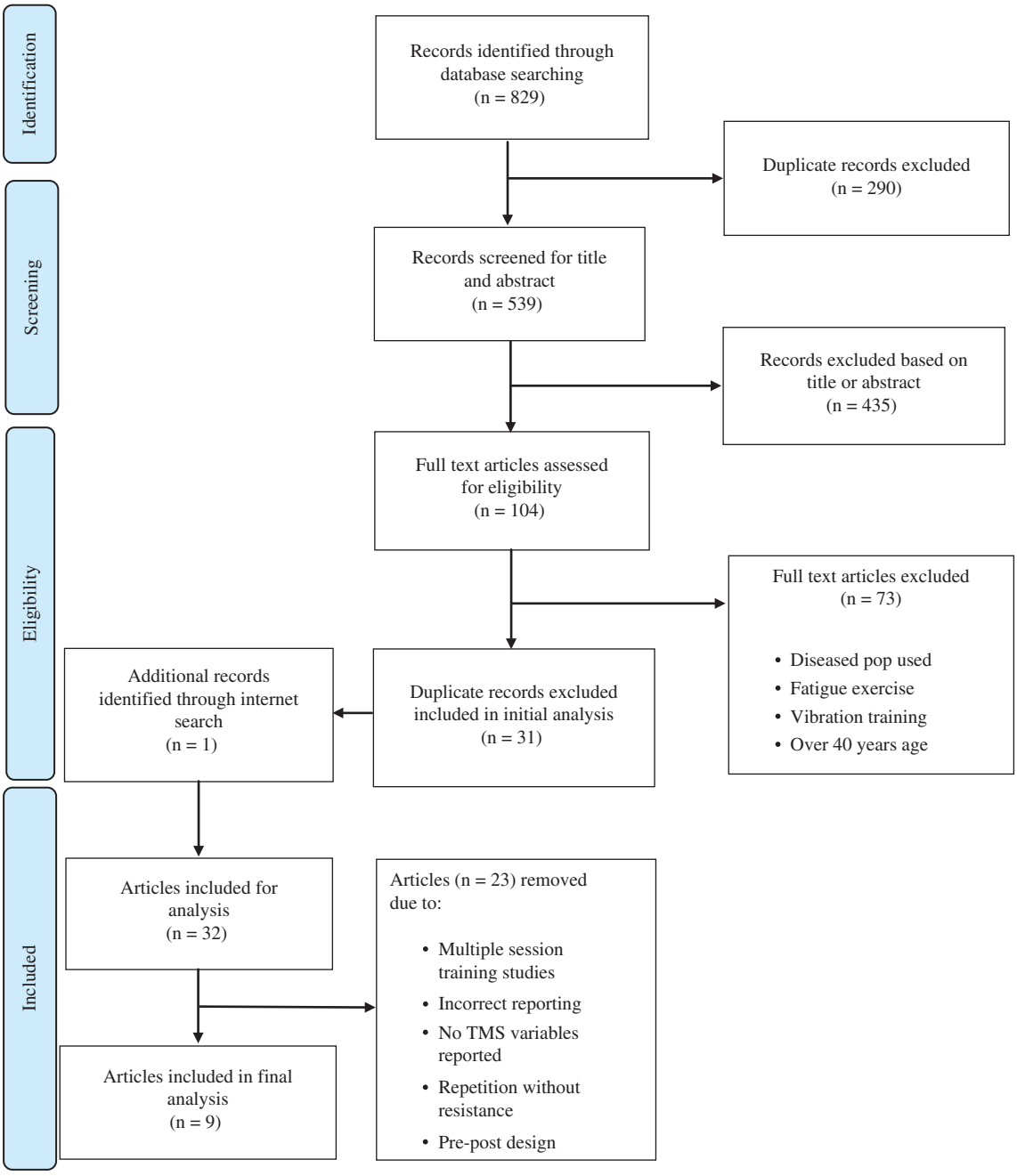

Figure 1: PRISMA study flow chart showing the process of study identification, screening, and evaluation of the eligibility of included studies.

(Downs and Black, 1998). This indicates a low-to-moderate quality of the studies; however, it must be noted that studies were not awarded points for criteria more relevant for randomised control trials and interventions studies, such as blinding of participants and statistical power. There was a high risk of bias across all studies (Figure 2). In particular, most publications were exposed to high risk for selection, performance, detection, attrition, and reporting biases (Table 3).

Corticospinal-motoneuronal excitability

MEP excitability

Complete corticospinal-motoneuronal data were extracted from nine studies (n = 107) that assessed MEP excitability post-training compared to control (n = 104). The pooled data indicated that after a single bout of strength training, MEP amplitude increases (SMD, 1.26; 95% CI, 0.88, 1.63;

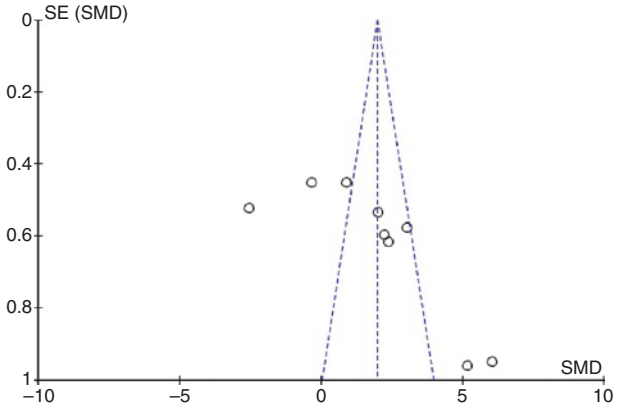

Figure 2: Forest plots showing the effect of acute strength exercise on corticospinal-motoneuronal excitability (nine studies, 107 subjects).
Std., Standardised mean difference; IV, inverse variance; Random, random effect model; CI, confidence interval; df, degrees of freedom; inconsistency statistic. Significance set at $p < 0.05$.

$p < 0.0001$), with the heterogeneity of results between the studies being high ($I^2 = 94\%$; Figures 2 and 3).

Cervicomedullary evoked potential amplitude

Data from three studies (n = 33) were pooled to identify changes in CMEP amplitude post-training compared to control (n = 30). The pooled data indicated that after a single bout of strength training, there was a significant change in CMEP amplitude (SMD, 4.47; 95% CI, 3.45, 5.49; $p < 0.0001$), with the heterogeneity of results between the studies being low ($I^2 = 3\%$, Figure 4).

Intracortical facilitation

Two studies (n = 28) from the same research group were used to analyse ICF after a single session of strength training. Analysis of the pooled data revealed an increase in ICF after a single session of strength training (SMD, 1.60; 95% CI, 0.18, 3.02; $p = 0.03$). There was high heterogeneity between studies ($I^2 = 80\%$, Figure 5).

Corticospinal-motoneuronal inhibition

Corticospinal silent period

Participant data from two studies (n = 28) were combined to assess the duration of the corticospinal silent period. After analysis, the pooled data indicated that a single bout of strength training, reduces the duration of the corticospinal silent period (SMD, –17.57; 95% CI, –21.12, –14.01; $p < 0.001$). There was extremely low heterogeneity between studies ($I^2 = 75\%$, Figure 6).

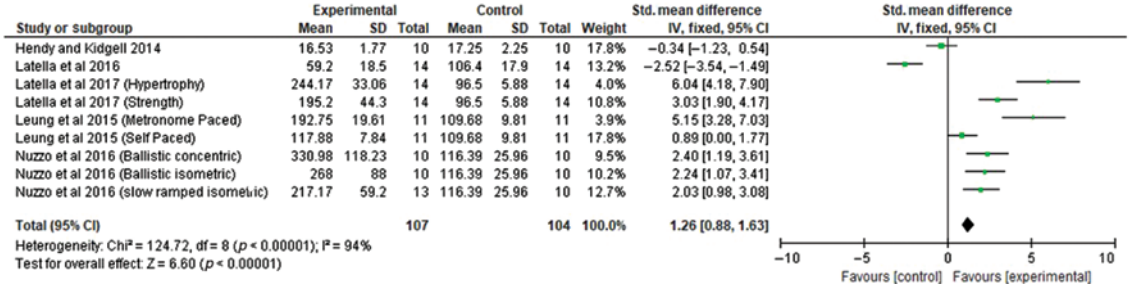

Figure 3: Forest plots showing the effect of acute strength exercise on the amplitude of MEPs (nine studies, 107 subjects).
Std., Standardised mean difference; IV, inverse variance; Random, random effect model; CI, confidence interval; df, degrees of freedom; inconsistency statistic. Significance set at $p < 0.05$.

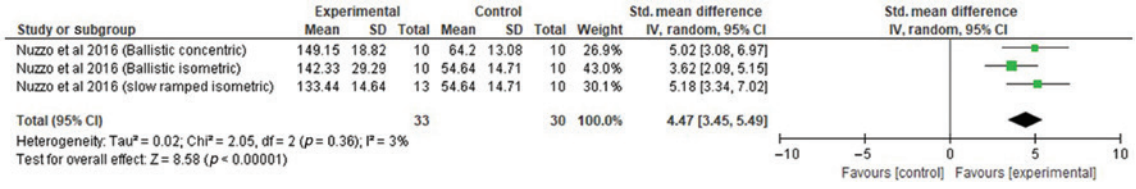

Figure 4: Forest plots showing the effect of acute strength exercise on the amplitude of cervicomedullary evoked potentials (three studies, 33 subjects).
Std., Standardised mean difference; IV, inverse variance; Random, random effect model; CI, confidence interval; df, degrees of freedom; inconsistency statistic. Significance set at $p < 0.05$.

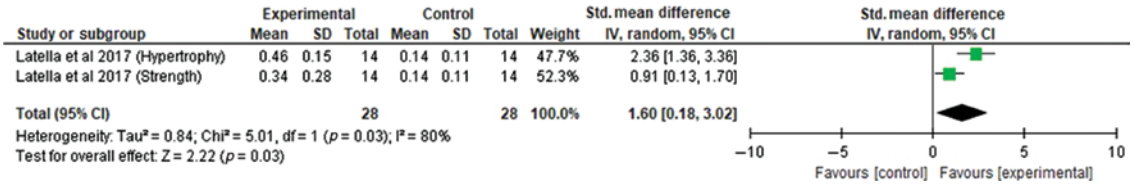

Figure 5: Forest plots showing the effect of acute strength exercise on ICF (two studies, 28 subjects).
Std., Standardised mean difference; IV, inverse variance; Random, random effect model; CI, confidence interval; df, degrees of freedom; inconsistency statistic. Significance set at $p < 0.05$.

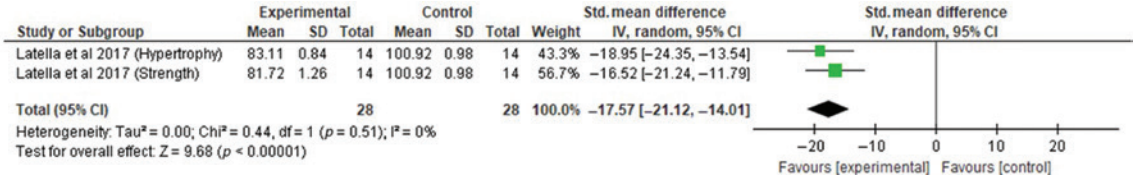

Figure 6: Forest plots showing the effect of acute strength exercise on corticospinal silent period duration (two studies, 28 subjects).
Std., Standardised mean difference; IV, inverse variance; Random, random effect model; CI, confidence interval; df, degrees of freedom; inconsistency statistic. Significance set at $p < 0.05$.

Short-interval intracortical inhibition

Five studies (n = 60) met the criteria for assessing SICI after a single bout of strength training. Pooled data revealed that SICI is not released (decreased) in the period immediately after a single session of strength training (SMD, 1.01; 95% CI, –1.67, 3.69; $p = 0.46$). The studies involved were highly heterogeneous ($I^2 = 96\%$, Figure 7).

Long-interval intracortical inhibition

Three studies (n = 42) were used to analyse LICI after a single session of strength training. Analysis of the pooled data revealed no changes in LICI after a single session of strength training (SMD, 0.50; 95% CI, –1.13, 2.13; $p = 0.55$). There was high heterogeneity between studies ($I^2 = 91\%$, Figure 8).

Discussion

The aim of this systematic review and meta-analysis was to examine whether a single session of strength training had any notable effect at the cortical level, specifically the excitability of the intracortical circuits of the M1 and the corticospinal-motoneuronal pathway, and/or effect at the spinal levels via excitability of corticospinal axons. Overall, this review found that there was a large effect (SMD, 1.26) for strength training to increase MEP amplitude and a very large effect (SMD, –17.57) for reducing the duration of the corticospinal silent period, showing that strength training increases the excitability and decreases inhibition of the corticospinal-motoneuronal pathway. Interestingly, this review also found that the excitability of the intracortical circuitry of the M1 was facilitated by strength training, as evidenced by a large increase in ICF (SMD, 1.60) and large increase in CMEP amplitude (SMD, 4.47), showing that

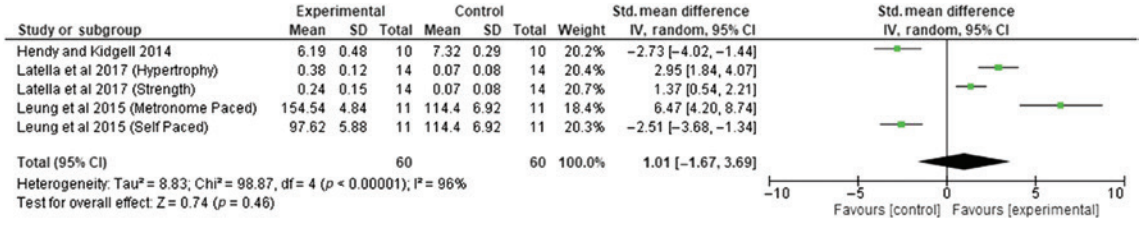

Figure 7: Forest plots showing the effect of acute strength exercise on SICI (five studies, 60 subjects).
Std., Standardised mean difference; IV, inverse variance; Random, random effect model; CI, confidence interval; df, degrees of freedom; inconsistency statistic. Significance set at $p < 0.05$.

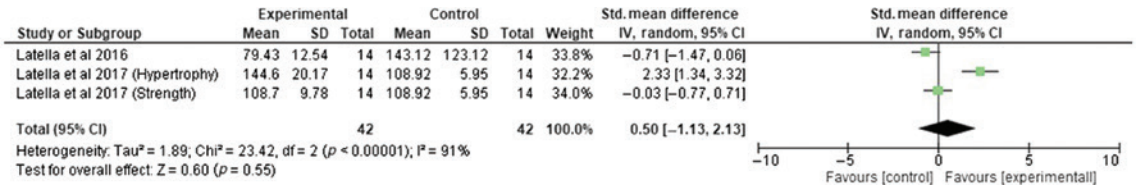

Figure 8: Forest plots showing the effect of acute strength exercise on LICI (three studies, 42 subjects).
Std., Standardised mean difference; IV, inverse variance; Random, random effect model; CI, confidence interval; df, degrees of freedom; inconsistency statistic. Significance set at $p < 0.05$.

strength training affects the excitability of corticospinal axons. Interestingly, the short and long latency intracortical inhibitory circuits remained unaffected by strength exercise (SICI SMD, 1.01; LICI SMD, 0.50).

These results suggest that a single session of strength training affects the excitability of both the corticospinal-motoneuronal pathway and the intrinsic circuitry of the M1, showing that there are subtle neurological changes from the M1 to the spinal cord. Such changes are likely to have important implications for strength development after long-term strength training. Despite these important findings, the quality assessment of studies to date revealed that the studies were of 'low to moderate' quality (Downs and Black, 1998) with an associated 'moderate to high' risk of bias (Higgins et al., 2011) and moderate to high heterogeneity. Future studies will need to address such methodological limitations to increase the overall quality and use a complimentary set of experimental techniques to provide objective data, which could include the collective use of techniques such as electroencephalography, functional magnetic resonance imaging, and TMS.

A single session of strength training increases the excitability of the corticospinal-motoneuronal pathway and the intracortical facilitatory circuits of M1

Previous studies have explored the effect of plasticity (via MEP excitability) and strength training over a longer term (e.g. three times per week for 2–4 weeks of strength training), to report the overall findings are inconsistent. Some studies reported increased MEPs (Griffin and Cafarelli, 2007; Weier et al., 2012), decreased (Carroll et al., 2002), or no change (Latella et al., 2012; Coombs et al., 2016). In fact, a recent systematic review and meta-analysis reported that the training-related effects of strength training had no overall effect on increasing MEP amplitude (Kidgell et al., 2017). In contrast, the pooled estimate obtained from the nine studies included in the current meta-analysis revealed a large effect (SMD, 1.26) for increased MEP amplitude in the period immediately after a *single* session of strength training. Furthermore, the enhancement of MEP amplitude was highly variable between studies and extends across a range of muscle groups that were exercised, including biceps brachii (Leung et al., 2015) and wrist flexors (Nuzzo et al., 2016); however, very few eligible studies assessed any lower limb muscles (Latella et al., 2017). Moreover, the increase in MEP amplitude was consistent across different types of muscle actions, with both isometric (Nuzzo et al., 2016) and isotonic (Leung et al., 2015; Latella et al., 2017) strength training eliciting an increase. These results suggest that the rapid increase in MEP amplitude after a single session may be transient and are possibly due to independent mechanisms, which closely resemble those associated with motor learning (Butefisch et al., 2000). Indeed, the role of motor learning in the early exposure to strength training may explain the disparity between the acute and chronic changes in MEP amplitude.

After a single bout of skill training, MEP amplitude is rapidly and transiently elevated (Cirillo et al., 2011), with the suggestion that early consolidation of a skill begins in the M1 from the first exposure to a new task (Muellbacher et al., 2002). In novice strength trainers, first exposure to a loaded strength training stimulus may be akin to skill training, and therefore MEP amplitude may increase as an early 'plastic' response to acquire and consolidate the task. However, it should be noted that, although motor performance improvements are often accompanied by MEP amplitude, the two are not always correlated (Carroll et al., 2008; Mason et al., 2017), and thus the complete functional significance of MEP increases after a strength training stimulus remains elusive. It is likely that the acute increase in MEP amplitude after a single session of strength training is to attenuate muscle fatigue generated through strength training (Latella et al., 2017). Furthermore, strength training-induced fatigue is accompanied by many physiological responses, which modify the

acute chemical environment, subsequently modulating changes in MEP amplitude and the intrinsic circuitry of the M1 (Goodall et al., 2018). Strength training is sufficient to induce increases in lactate, which has been associated with increases in MEP amplitude (Coco et al., 2010). In addition to changes in MEP amplitude, the pooled estimate for the effect of a single session of strength training modulating ICF revealed a large effect (SMD, 1.60). This finding suggests that strength training targets glutamatergic neuronal populations located specifically in the M1, revealing that the intracortical circuits of the M1 become facilitated (Di Lazzaro and Ziemann, 2013). This is an important new finding to the literature and has important clinical implications during periods of motor rehabilitation.

Although an increase in MEP amplitude represents a general increase in M1 excitability, it must be recognised that the amplitude of MEPs are influenced by several factors from the M1 to the muscle itself. For example, the excitability of the corticospinal and intracortical neurons that are activated by TMS and the efficacy of the synapses between these neurons can influence MEP amplitude (Mazzocchio et al., 1994; Ugawa et al., 1995). Furthermore, the excitability of interneurons located between corticospinal neurons and α-motoneurones, the efficacy of the corticospinal-motoneuronal synapses (Taylor and Martin, 2009; Bunday and Perez, 2012), and the excitability of the motoneurones themselves (Nielsen and Petersen, 1995; Di Lazzaro et al., 1998) all effect the amplitude of MEPs. In fact, this meta-analysis showed that strength training specifically affects the excitability of corticospinal axons, as CMEP amplitude increased, showing that the acute neuronal changes to strength training involve subtle changes along the entire neuroaxis (i.e. cortex to spinal cord).

A single session of strength training reduces the excitability of the inhibitory corticospinal-motoneuronal pathway, but has no effect on the excitability of the intracortical inhibitory circuits of M1

In addition to interacting with excitatory circuitry in the M1, a single session of strength training has been suggested to decrease intracortical inhibition, which likely contributes to the subsequent increase in excitatory drive to the α-motoneurones (Mazzocchio et al., 1994). Single-pulse TMS can measure inhibition via recording the duration of the corticospinal silent period, which is mediated by the neurotransmitter $GABA_B$ and indicates an interruption in volitional drive from the M1 and withdrawal of descending input to the spinal α-motoneurones (Chen et al., 1999; McDonnell et al., 2006). In contrast, SICI is derived from paired-pulse TMS and is synaptic in origin, mediated by GABAergic inhibitory neurones acting via $GABA_A$ receptors (Kujirai et al., 1993). A reduction in inhibition appears to be important for the expression of muscle strength (Clark et al., 2008, 2010, 2014; Kidgell et al., 2017); however, this meta-analysis revealed that only $GABA_B$-mediated intracortical circuits are affected by a single session of strength training. In the context of strength training, the observed immediate decrease corticospinal silent period duration may represent acquiring the skill of producing high levels of muscular force, in response to the initial training exposure. It has been suggested that an immediate reduction in the excitability of the inhibitory motor pathways may serve to increase 'motor focus', and therefore facilitate an increase in drive to muscle representations producing the intended movement. It is unclear why strength training had no effect on SICI, but given the small number of studies included and high level of variability across study estimates, there is a greater need to determine the cortical inhibitory responses following strength training.

Moreover, this review found that an acute bout of strength training had no effect on LICI, a confirmed $GABA_B$ circuit within the M1. Thus, to disentangle whether the result is through a lack of presence or is a product of a small number and low-quality studies, more thorough investigation of the long-intracortical inhibitory circuits after strength training is recommended.

Overall, the finding that inhibition is not reduced in the intrinsic circuitry of the M1 (e.g. SICI) after a single bout of strength training is in contrast with the evidence after both multiple sessions of strength training across a short-term muscle strength intervention (Kidgell et al., 2017). This suggests that changes in the intracortical inhibitory circuits of the M1 evolve over a greater period and may be important for strength development (Kidgell et al., 2017).

Limitations

Although this review has provided a novel appraisal of the acute corticospinal-motoneuronal responses to strength training, there are several limitations, which preclude stronger conclusions to be drawn. First, the overall volume of studies is low, particularly for neurophysiological measurements outside of MEP amplitude. Wider adoption of more diverse TMS analysis, for example, studies that incorporate corticospinal silent periods, SICI, LICI, ICF, CMEPs, and twitch forces, would significantly

strengthen the currently incomplete picture of the corticospinal-motoneuronal responses to strength training. Second, the studies eligible for the review originated from only four separate lab groups, and six of the studies shared authors who had previously published together in some capacity. This, paired with other factors such as nonreporting of how participants were randomly allocated to groups and nonblinding of data analysis, indicates a high potential for bias. Third, disparity in types of contraction, muscles used, and the loading and volume of training likely contribute to the high variability observed in this review. Overall, these issues likely overestimate the observed pooled effects in this review. In addition, because of the small numbers of studies that entered the meta-analysis, the findings should only be viewed as preliminary and therefore some caution should be used in the mechanistic interpretation of these data. Fourth, a wider, more robust view of the corticospinal-motoneuronal responses to strength training will only be complete with the analysis of other muscles, which contribute to force production, including synergists and antagonists. Moving beyond simple agonist measurements and including more diverse measures of corticospinal-motoneuronal function are necessary to comprehensively identify how the human nervous system contributes to force development. Finally, very few studies have made a valid attempt to link neuroplastic changes in the corticospinal-motoneuronal pathway and M1 changes to the behavioural outcomes.

Future direction and clinical implications

The ability to activate muscles and produce force is critical for many activities of daily living. For example, there is a good correlation that exists between muscle strength and several clinical outcomes, such as gait speed (Suzuki et al., 2002), decreased risk of falls (Spink et al., 2011), better balance (Moreland et al., 2004), and people with greater strength levels live longer (Legrand et al., 2014). Therefore, understanding the mechanisms that contribute to force development is important to provide targeted and effective guidelines for strength development during motor rehabilitation. This review has established in some capacity how the corticospinal-motoneuronal pathway and M1 responds to a single session of strength training. A single bout appears to increase MEP amplitude and decrease inhibition in the CNS by modifying the excitability of both $GABA_B$-mediated intracortical circuits via a reduction in the duration of the corticospinal silent period.

This review is an essential step towards understanding how the responses to a single session of strength training may accumulate to stimulate longer-term corticospinal-motoneuronal and M1 adaptations and ultimately lead to increases in muscle strength. It is feasible that each individual session comprises a necessary stage, which precedes permanent changes, particularly given that corticospinal inhibition is reduced after both single and multiple sessions (Kidgell et al., 2017). Furthermore, throughout a 4-week training program, when the M1 is disturbed via repetitive TMS after each session, cumulative strength gains are diminished (Hortobágyi et al., 2009). This not only emphasises the role of the M1 and corticospinal-motoneuronal pathway in strength development but also accentuates the role of corticospinal responses after a single session of strength training contributing to strength gains. Based on the results of this study and existing evidence, the acute changes after a single session of strength training may be a necessary precursor to more permanent synaptic plasticity, which accompanies long-term motor improvements. Precisely how these acute responses accumulate to create these adaptations remains unknown.

Conclusion

The results of this systematic review and meta-analysis reveal that a single session of strength training changes the excitability of the intracortical circuitry of the M1 towards facilitation (increased ICF and MEPs) and improves neural transmission along the corticospinal-motoneuronal pathway (increased CMEP excitability and reduced corticospinal inhibition). The results suggest that strength training may be a useful intervention that can be clinically useful to modulate intracortical circuits. These are important new findings that illustrate that the neurological responses to strength training involve the removal of inhibition from the M1 to the spinal cord and increase excitability from the M1 to the muscles acting as the first step towards the development of muscle strength.

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