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

Joel Mason (1), Dr Ashlyn K Frazer (1), Dr Alan J Pearce (2), Dr Alicia M Goodwill (3), Dr Glyn Howatson (4,5), Dr Shapour Jaberzadeh (1), and Dr Dawson J Kidgell (1)*

[1]Department of Physiotherapy, School of Primary Health Care, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Australia.

[2]Department of Rehabilitation, Nutrition and Sport, School of Allied Health, La Trobe University, Melbourne, Australia.

[3]School of Psychology, Australian Catholic University, Melbourne, Victoria, Australia.

[4]Faculty of Health and Life Sciences, Northumbria University, Newcastle-upon-Tyne, UK.

[5]Water Research Group, School of Environmental Sciences and Development, Northwest University, Potchefstroom, South Africa.

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Address for Corresponding author:

Dr Dawson J Kidgell

Department of Physiotherapy, School of Primary Health Care, Faculty of Medicine, Nursing and Health Science, Monash University, PO Box 527 Frankston, Victoria, Australia, 3199.

Email: dawson.kidgell@monash.edu

Abstract:

Several studies have used Transcranial Magnetic Stimulation (TMS) 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 corticospinal-motoneuronal pathway. A systematic review was completed tracking studies between January 1990 and May 2018. 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 following strength training compared to control, corticospinal excitability (SMD 1.26, 95% 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 (SICI; SMD 1.01, 95% CI -1.67, 3.69; $P = 0.46$; 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.

Introduction

It is well established that the human nervous system can modify its function in response to physical activity or experience (Kidgell et al., 2017; Katiuscia et al., 2009; Kleim et al., 2002). 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 a number of different ways, strength training has also been shown to influence plastic changes in the central nervous system (Frazer et al., 2017; Hendy and Kidgell, 2013; Leung et al., 2017; Mason et al., 2017; Nuzzo et al., 2016).

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 following a single session of strength training (Hendy and Kidgell, 2014; Latella et al., 2017; Selvanayagam et al., 2011; Nuzzo et al., 2016). Suggestions for this acute development of muscle strength have been attributed to neurological factors (Carroll et al., 2002; Kidgell et al., 2017). (Kidgell et al., 2010; Christie and Kamen, 2013; Griffin and Cafarelli, 2007; Carroll et al., 2002).

TMS has emerged as the leading candidate to provide insight into the synaptic activity of the cortico-cortical 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 following 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; Hendy and Kidgell, 2013; Mason et al., 2017; Christie and Kamen, 2013).

There are now a number of studies that have employed TMS to investigate the integrity of the corticospinal-motoneuronal pathway following a single session of strength training (Hendy and Kidgell, 2014; Brandner et al., 2015; Leung et al., 2015; Latella et al., 2018; Latella et al., 2016; Latella et al., 2017; Nuzzo et al., 2016; Selvanayagam et al., 2011). 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 following 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 following 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; Latella et al., 2017; Latella et al., 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 following an intervention; thus, stimulating the axons of corticospinal fibres assist to identify the level of synaptic modification. Cervicomedullary motor evoked potentials (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 following 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 are 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 $GABA_B$ receptor activity, following a single session of strength training is relatively limited and there is no clear consensus (Latella et al., 2017; Latella et al., 2018; Ruotsalainen et al., 2014). A tentative explanation for the discrepancy between studies likely resides in the parameters of the strength-training task, for example the muscles trained, TMS stimulus intensity used, training load, and type of strength training (paced, non-paced, 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., 2018; Latella et al., 2017; Latella et al., 2016). There is now evidence that shows SICI is reduced following a single session of strength training (Latella et al., 2018; Latella et al., 2017; Latella et al., 2016; Leung et al., 2015; Hendy and Kidgell, 2014; Brandner et al., 2015), however, the overall consensus of these changes is not clear and warrants a systematic investigation to detrmine 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 following a single session of strength training (Latella et al., 2018; Latella et al., 2017; Latella et al., 2016) 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, multi-session strength training programs (Kidgell et al., 2017) and other forms of motor training (Dayan and Cohen, 2011; Manca et a., 2018) are now well established, no such consensus currently exists for the acute corticospinal-motoneuronal responses following 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 databases 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'.

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

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. Following 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 were 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 humans of either gender between the ages of 18 and 40 years of age; **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 one hour 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 short- and long-interval intracortical inhibition and intracortical facilitation. Exclusion criteria established included diseased populations, non-English publications, non-peer reviewed proceedings and theses, as well as studies, which employed non-typical 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. Further, 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, gender), 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 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 cervicomedullary evoked potentials [CMEPs] (Taylor, 2006). Paired-pulse measure in the meta-analysis was 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 post-intervention 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 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 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 cut off points corresponding to low (25%), moderate (50%) and high (75%) heterogeneity. Funnel plots assessed publication bias however, due to 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 alpha level of $p<0.05$ to determine significance.

Results

Figure 1 displays 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. Following 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 non-conventional strength training methods such as vibration training and fatiguing exercise. After additional searching 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 (Downs & 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 randomized 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 9 studies (n = 107) that assessed MEP excitability post-training compared to control (n – 104). The pooled data indicated that following a single bout of strength training, MEP amplitude increases (SMD 1.26, 95% CI 0.88, 1.63, P < 0.0001), with the heterogeneity of results between the studies being high (I^2 = 94%; Fig. 2 and Fig. 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 following 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%, Fig. 4).

Intracortical Facilitation **-** Two studies (n = 28) from the same research group were used to analyse ICF following a single session of strength training. Analysis of the pooled data revealed an increase in ICF following 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%, Fig. 5).

Corticospinal-motoneuronal Inhibition

Corticospinal Silent Period **-** Participant data from 2 studies (n = 28) were combined to assess the duration of the corticospinal silent period. Following analysis, the pooled data indicated that, following a single bout of strength training, there was a reduction in the duration of the corticospinal silent period duration (SMD -17.57, 95% CI -21.12, -14.01; P < 0.001). There was extremely low heterogeneity between studies (I^2 = 75%, Fig. 6).

Short-interval Intracortical Inhibition **-** Five studies (n = 60) met the criteria for assessing SICI following a single bout of strength training. Pooled data revealed that SICI is not released (decreased) in the period immediately following a single session of strength training (SMD 1.01, CI 95% -1.67, 3.69; P = 0.46). The studies involved were highly heterogeneous (I^2 = 96%, Fig. 7).

Long-interval Intracortical Inhibition **-** Three studies (n = 42) were used to analyse LICI following a single session of strength training. Analysis of the pooled data revealed no changes in LICI following 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%, Fig. 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 CMEP amplitude (SMD 4.47), showing that 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 following 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 (EEG), functional magnetic resonance imaging (fMRI) 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. 3 times per week for 2-4 weeks of strength training),

to report the overall findings are inconsistent. Some studies reported increased MEPs (Weier et al., 2012; Griffin and Cafarelli, 2007), decreased (Carroll et al., 2002) or no change (Coombs et al., 2016; Latella et al., 2012). 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 9 studies included in the current meta-analysis, revealed a large effect (SMD 1.26) for increased MEP amplitude in the period immediately following 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 (Latella et al., 2017; Leung et al., 2015) strength training eliciting an increase. These results suggest that the rapid increase in MEP amplitude following 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 disparity between the acute and chronic changes in MEP amplitude.

Following 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 in order 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 following a strength stimulus remains elusive. It is likely that the acute increase in MEP amplitude following a single session of strength training is to attenuate muscle fatigue generated through strength training (Latella et al., 2017). Further, strength training-induced fatigue is accompanied by a number of 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 suggest 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). Further, the excitability of interneurons located between corticospinal neurons and α-motoneurones, the efficacy of the corticospinal-motoneuronal synapses (Bunday and Perez, 2012; Taylor and Martin, 2009); 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 gamma-aminobutryic acid-$_B$ ($GABA_B$) and indicates an interruption in volitional drive from the M1 and withdrawal of descending input to the spinal α-motoneurones (McDonnell et al., 2006; Chen et al., 1999). On the other hand, 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; Clark et al., 2010; Clark et al., 2014; Kidgell et al., 2017); however this meta-analysis revealed that both $GABA_A$ and $GABA_B$ mediated intracortical circuits are not affected by a single session of 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, in order 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 following strength training is recommended.

Overall, the finding that inhibition is not reduced in the intrinsic circuitry of the M1 (e.g. SICI) following a single strength training is in contrast with the evidence following both

multiple sessions of strength training across a short-term muscle strength intervention (Kidgell et al., 2017). This suggest 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. Firstly, 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 which 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. Secondly, 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 non-reporting of how participants were randomly allocated to groups and non-blinding 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 contributes 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 in order 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 a number of 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, in order 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 $GABA_A$ and $GABA_B$ mediated intracortical circuits.

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 and SICI is reduced following both single and multiple sessions (Kidgell et al., 2017). Further, throughout a four-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 following a single session of strength training contributing to

strength gains. Based on the results of this study and existing evidence, the acute changes following 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 involves the removal of inhibition from the M1 to the spinal cord and increases excitability from the M1 to the muscles acting as the first step towards the development of muscle strength.

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Table legends.

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

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

Table 3. Cochrane risk of bias.

Table 1: Search strategy examples used to yield the 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 Timespan = 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 Timespan = 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 Timespan = 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 Timespan = 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 Timespan = 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 Timespan = 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 Timespan = 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 Timespan = 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. Intracortcial 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	

Table 2.

Study	Country	Design	Evidence Level	Training	Sample Size	Participant characteristics	Age Mean ±SD (Yr)	Sampling	Key DV	Key Measure(s)	Results	Score
Hendy & Kidgell 2014	Australia	Pre-test-post-test crossover	III-1	4sets, 6-8 reps @ 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	Pre-test-post-test crossover	III-1	5sets, 3 re[s @94% 1-RM	14	Previous training history, healthy young	26.±5	Random	Corticospinal excitability, intracortical facilitation, long-interval intracortical inhibition	MEP amplitude, ratio, ICF ratio, LICI ratio	↓ MEP amplitude 44%, ↑ICF 36%, ↑ LICI 33%	20
Latella et al 2017 (hypertrophy)	Australia	Pre-test-post-test crossover	III-1	3sets, 12 reps @67% 1-RM	14	Previous training history, healthy young	26.±5	Random	Corticospinal excitability and inhibition, intracortical facilitation, long-interval intracortical inhibition	MEPamplitude, 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 Pre-test-Post-test	III-1	4sets, 6-8 reps @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 Pre-test-Post-test	III-1	4sets, 6-8 reps @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	Pre-test-post-test crossover	III-1	12 sets, 8 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	Pre-test-post-test crossover	III-1	12 sets, 8 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	Pre-test-post-test crossover	III-1	12 sets, 8 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 & Kidgell 2014	-	+	-	+	-	-	Same lab group as 2 other subgroups.
Latella 2016	-	+	+	+	-	-	Same lab group as 2 other subgroups
Latella 2017 (strength)	-	+	+	+	-	-	Same lab group as 2 other subgroups.
Latella 2017 (hypertrophy)	-	+	+	+	-	-	Same lab group as 2 other subgroups
Leung 2015 (metronome paced)	-	+	+	+	-	-	Same lab group as 2 other subgroups.
Leung 2015 (self-paced)	-	+	+	+	-	-	Same lab group as 2 other subgroups.
Nuzzo 2016 (ballistic isometric	-	+	+	+	-	-	Same lab group as 1 other subgroups.
Nuzzo 2016 (ballistic concentric)	-	+	+	+	-	-	Same lab group as 1 other subgroups.
Nuzzo 2016 (slow ramped)	-	+	+	+	-	-	Same lab group as 1 other subgroups..

+, high risk of bias; -, low risk of bias; ?, unclear risk of bias. Criteria established from the Cochran Collaboration tool for assessing risk of bias.

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

Figure 2. Funnel plot displaying the risk for publication bias in the 9 studies included.

Figure 3. Forest plots showing the effect of acute strength exercise on corticospinal-motoneuronal excitability (9 studies, 107 subjects). Std. standardized 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 cervico-medullary evoked potentials (3 studies, 33 subjects). Std. standardized 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 intracortical facilitation (2 studies, 28 subjects). Std. standardized 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 (2 studies, 28 subjects). Std. standardized 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 7. Forest plots showing the effect of acute strength exercise on short-interval intracortical inhibition (5 studies, 60 subjects). Std. standardized 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 long-interval intracortical inhibition (3 studies, 42 subjects). Std. standardized 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 1: PRISMA flowchart of studies included in the review.

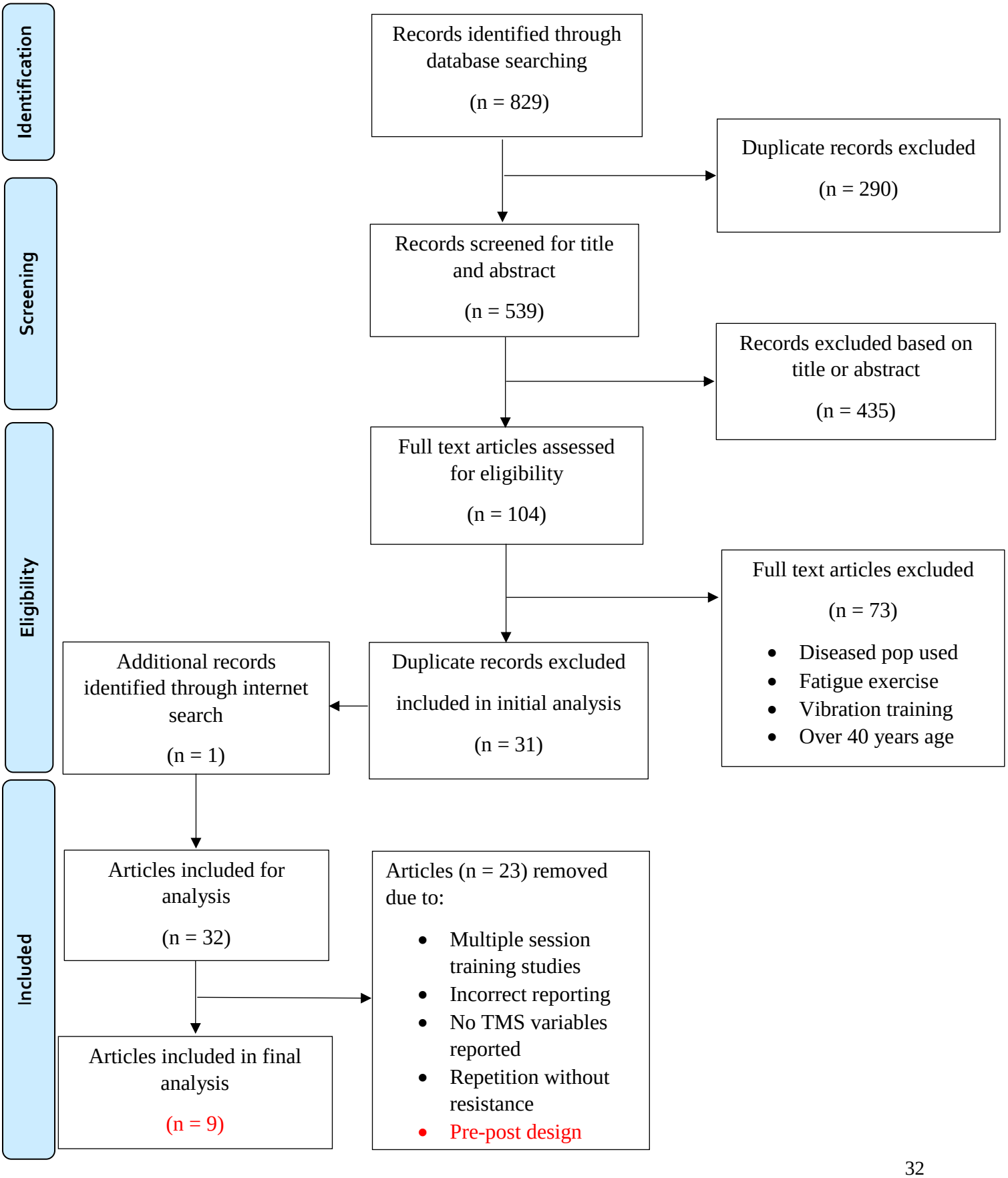

Figure 2. Funnel plot displaying the risk for publication bias in the 9 studies included.

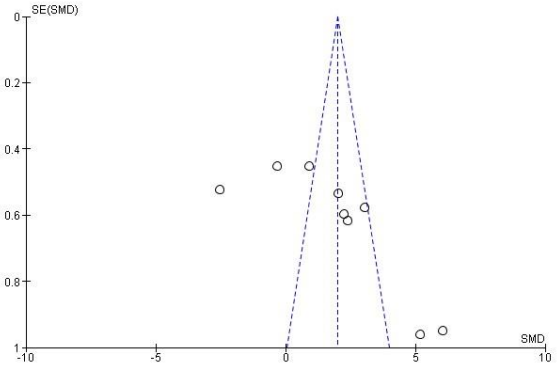

Figure 3. Forest plots showing the effect of acute strength exercise on corticospinal-motoneuronal excitability (9 studies, 107 subjects). Std. standardized mean difference; IV, inverse variance; Random, random effect model; CI, confidence interval; df, degrees of freedom; inconsistency statistic. Significance set at $p<0.05$.

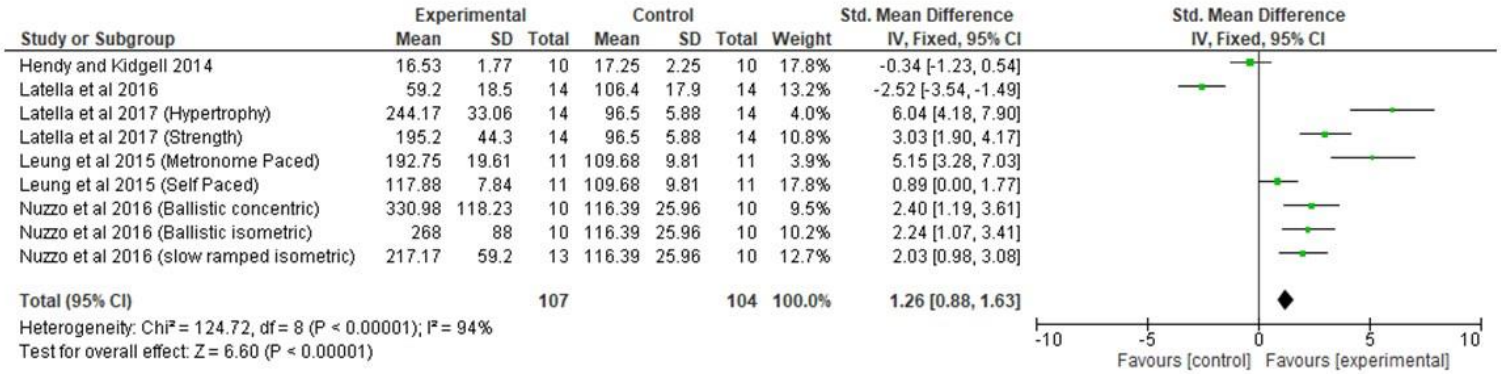

Figure 4. Forest plots showing the effect of acute strength exercise on the amplitude of cervico-medullary evoked potentials (3 studies, 33 subjects). Std. standardized mean difference; IV, inverse variance; Random, random effect model; CI, confidence interval; df, degrees of freedom; inconsistency statistic. Significance set at $p<0.05$.

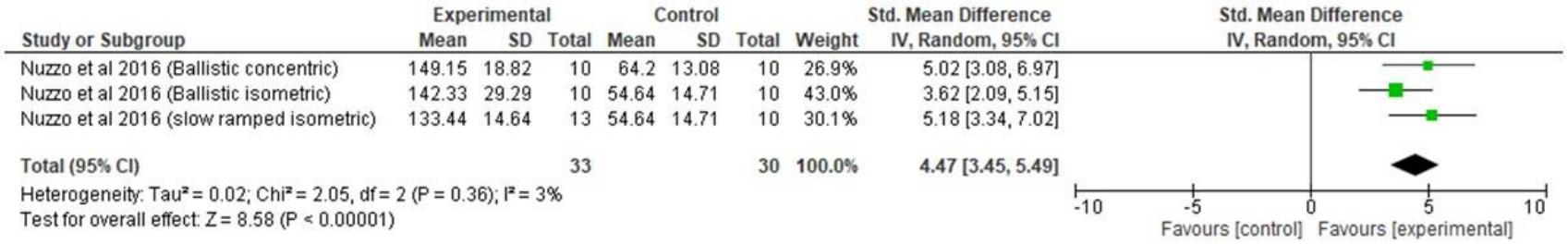

Figure 5. Forest plots showing the effect of acute strength exercise on intracortical facilitation (2 studies, 28 subjects). Std. standardized mean difference; IV, inverse variance; Random, random effect model; CI, confidence interval; df, degrees of freedom; inconsistency statistic. Significance set at $p<0.05$.

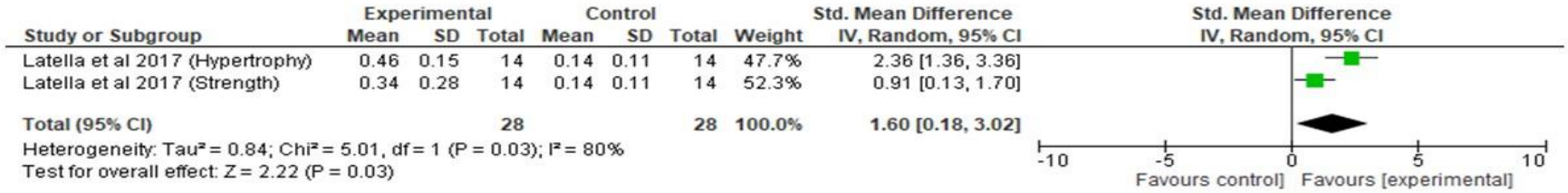

Figure 6. Forest plots showing the effect of acute strength exercise on corticospinal silent period duration (2 studies, 28 subjects). Std. standardized mean difference; IV, inverse variance; Random, random effect model; CI, confidence interval; df, degrees of freedom; inconsistency statistic. Significance set at $p<0.05$.

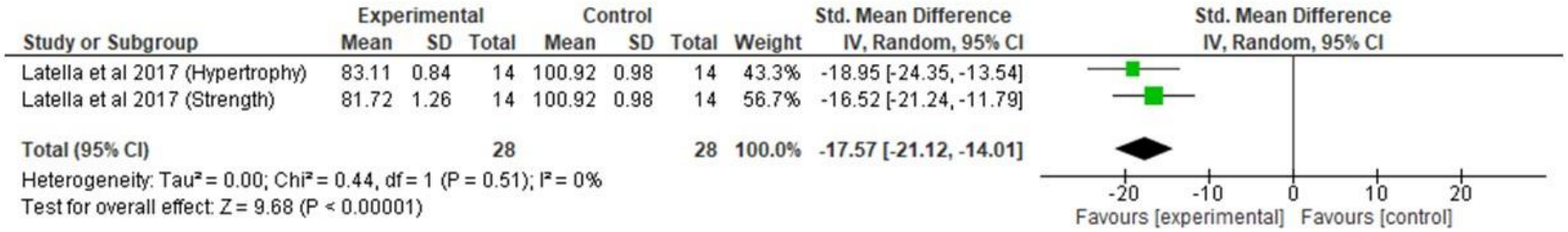

Figure 7. Forest plots showing the effect of acute strength exercise on short-interval intracortical inhibition (5 studies, 60 subjects). Std. standardized mean difference; IV, inverse variance; Random, random effect model; CI, confidence interval; df, degrees of freedom; inconsistency statistic. Significance set at $p<0.05$.

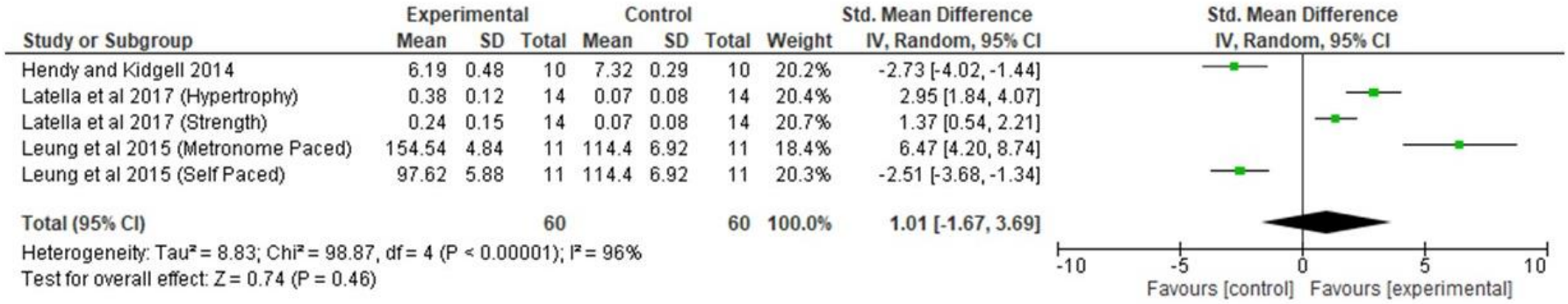

Figure 8. Forest plots showing the effect of acute strength exercise on long-interval intracortical inhibition (3 studies, 42 subjects). Std. standardized mean difference; IV, inverse variance; Random, random effect model; CI, confidence interval; df, degrees of freedom; inconsistency statistic. Significance set at $p<0.05$.