**Determining the sites of neural adaptations to resistance training: A systematic review and meta-analysis.**

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**Running head:** Neural adaptations to resistance training.

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**Abstract**

***Background:*** Resistance-training causes changes in the central nervous system (CNS); however, the sites of these adaptations remain unclear. ***Objective:*** To determine sites of neural adaptation to resistance-training by conducting a systematic review and meta-analysis on the cortical and subcortical responses to resistance-training. ***Methods:*** Evidence from randomized controlled trials (RCTs) that focused on neural adaptations to resistance-training were pooled to assess effect estimates for changes in strength, cortical and subcortical adaptations. ***Results:*** The magnitude of strength gain in 30 RCTs ($n$ = 623) reported a standardised mean difference (SMD) of 0.67 (95% CI 0.41, 0.94; $P$ < 0.001) that measured at least one cortical/subcortical neural adaptation which included: motor evoked potentials (MEP; 19 studies); silent period (SP; 7 studies); short-interval intracortical inhibition (SICI; 7 studies); cervicomedullary evoked potentials (CMEP; 1 study); transcranial magnetic stimulation voluntary activation ($VA_{TMS}$; 2 studies); H-reflex (10 studies) and V-wave amplitudes (5 studies). The MEP amplitude during voluntary contraction was greater following resistance-training (SMD 0.55; 95% CI 0.27, 0.84; $P$ < 0.001, $n$ = 271); but remained unchanged during rest (SMD 0.49; 95% CI -0.68, 1.66; $P$ = 0.41, $n$ = 114). Both SP (SMD 0.65; 95% CI 0.29, 1.01; $P$ < 0.001, $n$ = 184) and active SICI (SMD 0.68; 95% CI 0.14, 1.23; $P$ = 0.01, $n$ = 102) decreased, but resting SICI remained unchanged (SMD 0.26; 95% CI -0.29, 0.81; $P$ = 0.35, $n$ = 52). Resistance-training improved neural drive as measured by V-wave amplitude (SMD 0.62; 95% CI 0.14, 1.10; $P$ = 0.01, $n$ = 101), but H-reflex at rest (SMD 0.16; 95% CI 0.36, 0.68; $P$ = 0.56; $n$ = 57), during contraction (SMD 0.15; 95% CI -0.18, 0.48; $P$ = 0.38, $n$ = 142) and $VA_{TMS}$ (MD 1.41; 95% CI -4.37, 7.20; $P$ = 0.63, $n$ = 44) remained unchanged. ***Conclusion:*** There are subtle neural adaptations following resistance-training involving both cortical and subcortical adaptations that act to increase motoneurone activation and contribute to the training-related increase in muscle strength.

**Key Points:**

1. Resistance training induces neural adaptations that are comprised of subtle adaptations that include motor cortex plasticity, spinal cord plasticity and changes in motor unit activation.
2. The predominant site of neural adaptation appears to be at the level of the primary motor cortex due to changes in the level of excitation and inhibition in motor circuits.
3. Collectively, both cortical and subcortical adaptations to resistance training act to increase motoneurone activation, which increases neural drive and, therefore, a contributing mechanism for the training-related increase in muscle strength.

## 1 INTRODUCTION

It is axiomatic that changes in the nervous system contribute to the development of muscular strength following a period of resistance training [1, 2]. Subtle changes within the nervous system have been suggested to account for increases in muscular strength because strength increases occur in the absence of detectable muscle hypertrophy [3]. Several lines of evidence reveal that the rapid gain in muscular strength during the early phases of a resistance training program is associated with increased ability to activate the muscles [4]. In fact, early evidence was mostly derived from changes in muscle activation as detected with surface electromyography (SEMG). An increase in the amplitude of the SEMG signal has, by default, been interpreted as an increase in efferent motor output from cortical motor areas [5]. However, more recently, to overcome the limitations of SEMG [6], studies are increasingly using single motor unit recordings [7, 8], evoked spinal reflex responses, including the H-reflex and V-wave [9] and, more recently, non-invasive brain stimulation techniques, including transcranial magnetic stimulation (TMS) [10], cervicomedullary stimulation [11] and voluntary activation using TMS ($VA_{TMS}$) [12, 13]. Although these techniques have increased our understanding of the changes in the nervous system following chronic resistance training, there still remains much confusion as to which elements within the nervous system account for the strength increases observed [14].

There is good evidence to show that there are increases in the amplitude of the SEMG signal as a result of resistance training [3, 4, 9, 15]. Although earlier reports [15] suggested that the increase in SEMG occurs in the absence of any detectable changes in muscle hypertrophy, recent evidence suggested that detectable changes in muscle hypertrophy and SEMG occur within three weeks of a resistance training program [16, 17, 18, 19]. Notwithstanding, some studies have failed to observe any changes in the SEMG signal [20-23], although an authorative review suggested that changes in the amplitude of the SEMG signal is of limited value [6] because of challenges associated in retrieving the neural activation signal embedded in the SEMG. In general, the SEMG signal is not sensitive to small changes in motor unit activity and, therefore, underestimates motor unit activity due to signal cancellation [6]. The ideal method to study motor unit behaviour is to record the discharge rate of identifiable motor units using indwelling electrodes [6]. Using this invasive technique, several studies reported that resistance training increased motor unit activation [24, 25, 26]. For example, six weeks of resistance training increased strength by 33%, which was accompanied by a 15% increase in motor unit discharge rate in young adults, and by 49% in older adults [25]. This finding was also supported by Van Cutsem et al. [26] following 12 weeks of ballistic resistance training of the tibialis anterior. Both rate of force development and the amplitude of the SEMG increased, which were associated with an increase in the instantaneous discharge rate of the motor units [26]. Further, resistance training also yielded an increase (from 5 to 33%) in the number of motor units that discharged with brief interspike intervals (<5 ms). These studies suggest that resistance training can alter the discharge properties of motor units that represent one of potentially several neural adaptations to resistance training.

Outside of SEMG and motor unit studies, there has been an attempt to investigate changes in reflex physiology following resistance training that provide evidence for changes in spinal cord excitability/inhibition. The

Hoffman's or H-reflex can be used to evaluate the excitability of spinal alpha motoneurones and the efficacy of Ia afferent synapses. However, it should be noted that the magnitude of the H-reflex response is influenced by the level of presynaptic inhibition, which limits the interpretation of this technique as a quantifiable measure of motoneurone excitability [9]. Further, there is some degree of inherent variability in the H-reflex, which makes it difficult to compare significant changes following interventions and few studies use normalisation procedures, which further increases the difficulty in examining changes in H-reflex activity following an intervention. Despite these limitations, there have been no reports of an increase in H-reflex amplitudes at rest following resistance training [9, 27-37]. Conversely, H-reflex amplitudes recorded during voluntary contraction are inconsistent following resistance training, with some studies reporting increased H-reflex amplitudes [9, 29, 30, 35], and other studies reporting no changes [28, 31-33, 36, 37].

The volitional or V-wave is a measure that reflects the overall degree of efferent motor output from the alpha motoneurone pool. Increases in V-wave amplitude following resistance training have been frequently cited as evidence of increased efferent drive and subsequently enhanced activation of the motoneurone pool. There has also been an inclination to attribute increases in motoneurone activation as an adaptation that occurs at a supraspinal level, particularly when V-wave changes are observed in parallel with H-reflexes [9, 28]. However, a caveat to this interpretation is that the V-wave is an indirect measure of the potential role of cortical mechanisms contributing to efferent neural drive. In addition, the amplitude of the V-wave is influenced by several factors, including the number and firing rate of motoneurones that are involved in the voluntary contraction, the responsiveness of the motoneurones and the efficacy of synaptic transmission between 1a afferents and the motoneurones. Because the V-wave, like the H-reflex, is largely a monosynaptic reflex circuit from the 1a afferents to motoneurones, any change in V-wave amplitude could simply be due to a change in synaptic transmission (either 1a excitation or disynaptic inhibition) [9, 28].

In an attempt to overcome the limitations of reflex studies, TMS has emerged as a technique to provide insight into the synaptic activity of the cortico-cortical circuitry of the primary motor cortex (M1) following resistance training [14]. Experiments have examined the effect of resistance training on corticospinal excitability [10, 38-41], corticospinal inhibition [41-44] and intracortical inhibition and facilitation [40, 43, 45-47]. TMS involves placing a magnetic coil on the scalp positioned over the M1. The current generated creates a magnetic field, which induces an electric field in the M1 which stimulates the underlying neurones. TMS activates the axons of corticospinal neurones and intracortical neurones that synapse with the cell bodies of corticospinal cells [14]. Because TMS activates several neuronal elements within the M1, it produces multiple descending volleys (D-waves and I-waves) that occur as a result of direct and indirect activation of corticospinal axons [14]. These descending volleys activate alpha-motoneurones, causing a muscle response termed the motor-evoked potential (MEP). In general, the size of the MEP is a measure of corticospinal excitability. When a MEP is recorded during voluntary muscle activation, there is a pause in the ongoing SEMG signal which is termed the silent period (SP); this is a measure of corticospinal inhibition. The SP is mediated by the neurotransmitter gamma-aminobutyric acid-B (GABA-$_B$) and indicates an interruption in volitional drive from the M1 (i.e., neural drive) and withdrawal of descending input to the spinal motoneurone pool [14]. The SP can be used as a proxy measure for M1 excitability, particularly when reductions are observed following an intervention [41-44]. Although single-pulse

TMS is used to determine synaptic efficacy of the M1 and corticospinal tract, it does have limitations as it is unable to examine the excitability of the intracortical micro-circuits of the M1 [10]. Paired-pulse TMS allows for an assessment of the physiology of the intrinsic intra-cortical connections within the M1 following resistance training [14]. Depending on the inter-stimulus interval between the conditioning and test pulse, the excitability of the intracortical inhibitory (e.g., 2-5 ms) and long intracortical inhibitory (e.g., 100-150 ms) circuits of the M1 can be examined providing important information about the effects of resistance training on the GABA-ergic system [14]. Thus, using TMS can provide an important insight into how the M1 and corticospinal tract might be modulated following resistance training. The use of TMS and TMS cortical voluntary activation ($VA_{TMS}$) can provide a more robust measure of the cortico-cortical circuits of the M1 that underpin strength development when compared to the V-wave. However, because single-pulse and paired-pulse TMS generate MEPs, unfortunately, MEP amplitudes are influenced by several factors. Some of these factors originate with thin the M1 itself, the spinal cord and the muscle. Factors known to influence MEPs include the efficacy of synapses between intracortical and corticospinal neurones, the excitability of interneurones and motoneurones at the level of the spinal cord (including the efficacy of their synapses), the excitability of the motoneurones themselves, and peripheral factors such as the excitability of motor axons and the sarcolemma. Therefore careful consideration is required when interpreting TMS data following an intervention, as TMS is unable to identify the locus of adaptation.

Recently, we demonstrated that resistance training had an overall effect on reducing inhibition in the descending motor pathways, suggesting reduced inhibition could be important for strength gain [14]. However, a limitation of this previous meta-analysis was that it was unable to determine the site of adaptation as it only included studies that had used TMS to evaluate the neural adaptations to resistance training. There are now techniques that can provide additional insight into the neural adaptations to resistance training, including cervicomedullary stimulation and $VA_{TMS}$ [11, 13]. Cervicomedullary motor evoked potentials (CMEPs) can be generated subcortically via electrical stimulation at the cervicomedullary junction. When an electrical current passes through electrodes positioned on the mastoid processes, it evokes a descending volley which is captured using SEMG [11]. Because cervicomedullary stimulation is delivered inferior to the level of the M1, it is regarded as a measure of spinal excitability [11]. By comparing changes in CMEP and MEP amplitudes following resistance training, researchers are able to infer whether increases in excitability occur at a cortical or spinal level, or both.

The magnitude of efferent drive to a muscle is termed ‘voluntary activation’ and it is determined by interpolation of a single supramaximal electrical stimulus to the motor nerve during an isometric voluntary contraction [48]. If there is an increase in the force produced as a result of electrical stimulation, efferent drive is suggested to be incomplete. However, twitch interpolation is unable to identify the location of any impairment in efferent drive (cortical or sub-cortical) [13]. To overcome this, TMS has been employed to measure the net motor output from the M1 (i.e., $VA_{TMS}$), which can provide some insight into impaired efferent motor output [49, 50]. Unlike twitch interpolation, the presence of a superimposed twitch force produced by a supra-threshold TMS pulse during a maximum voluntary contraction (MVC) indicates a failure in efferent output at the level of the M1 [50]. At present, there are inconsistent findings regarding the effect of resistance training on $VA_{TMS}$ [12, 13].

In summary, there are multiple elements in the nervous system that adapt and contribute to strength gains following chronic resistance training. However, at present, the body of evidence is not clear, and hence a systematic review with meta-analysis has the potential to determine the contributing elements of the nervous system to the development of muscular strength following chronic resistance training. To our knowledge, there are no systematic reviews that have examined both the cortical and subcortical mechanisms that are associated with increased muscular strength following resistance training. Determining the potential sites of neural adaptations to resistance training will provide new knowledge about the underlying mechanisms of strength development, which have implications for exercise prescription and add context to the clinical use of resistance training. Therefore, the present systematic review examined the hypothesis that the neural adaptations accompanying increased muscular strength likely arise from subtle changes along the entire neuroaxis, with contributions from both cortical and subcortical mechanisms.

## 2 METHODS

### 2.1 Literature Search Strategy

A standardised search strategy (Electronic Supplementary Material Table S1') used the following electronic databases: Cochrane Library, CINAHL, EMBASE, PsycINFO, PubMed/MEDLINE, Science Direct, SciVerse, SCOPUS, SPORTDiscus and Web of Science from inception until the last week of August 2019. The search was conducted combining "resistance training" and its synonyms ("strength 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', 'cortical silent period', 'short-interval intracortical inhibition', 'cervicomedullary evoked potential', 'twitch amplitude', voluntary activation', 'H-reflex' and 'V-wave'.

The databases were searched from inception until 10 September 2019. References found from previously published literature were also searched. Figure 1 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 [51]. While commonly used to report on randomised trials, PRISMA has been used to systematically review quasi-experimental research [52].

### 2.2 Selection of Studies

The initial search was undertaken by two of the authors (US and SR). All titles and corresponding abstracts were retrieved and then screened. Any items that were deemed outside the scope of the present meta-analysis were removed. Following screening of titles and abstracts, two authors (AKF and DJK) independently selected and reviewed all included articles. At this point, all duplicated studies were removed. Any full-text articles that satisfied the inclusion criteria were read and eligible studies were then included in the meta-analysis. In the case

of disagreement, both assessors reviewed each study independently, and a third assessor (GH) resolved any discrepancies.

### 2.3 Eligibility Criteria – Exclusion and Inclusion

Studies were considered for review if they met the following criteria: 1) untrained healthy young humans of either sex between the ages of 18 and 40; 2) training intervention involved two or more weeks of strength or resistance training; 3) resistance training involved a training-load that was greater than 50% of the maximal load; 4) studies must have compared an intervention to a control group; 5) stimulation of M1 at baseline and post-training to quantify changes in corticospinal excitability and inhibition through single-pulse TMS measures which included MEPs (recorded in both active and resting muscles), CMEPs, $VA_{TMS}$, and reflex measures including H-reflex (recorded in both active and resting muscles) and V-wave. It should be noted that studies that examined at least one of the above electrophysiological measures were included. Studies could also be included if they used paired-pulse TMS at baseline and post-training to measure short- and long-interval intracortical inhibition (SICI and LICI) and intracortical facilitation (ICF). Exclusion criteria included diseased populations, no comparison to a control group, non-English publications, non-peer reviewed proceedings and theses, as well as training studies which employed non-typical resistance 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 baseline.

### 2.4 Quality Assessment and Risk of Bias

Two reviewers (US and SR) used a modified version of the Downs and Black [52] checklist (Table 1) to assess the quality of included studies. Further, the Cochrane Risk of Bias tool [53, 54] 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 (Fig. 2). 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.

### 2.5 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 resistance training protocol (isometric, dynamic, eccentric, concentric, isometric, upper body, lower body). In addition, the following outcome measures from included studies were extracted from the available text: strength, MEP amplitude (peak-to-peak waveform and expressed either as a raw amplitude, percentage of peripheral M-wave amplitude, relative to motor threshold, $MEP_{MAX}$ or arbitrary units obtained from a stimulus-response curve), silent period (quantified as the duration from

the onset of MEP waveform to the return of uninterrupted SEMG activity) and cervicomedullary evoked potentials [CMEPs] area and $VA_{TMS}$ expressed as a percentage. SICI was assessed to examine intracortical inhibition, which was calculated as the ratio of the test stimulus and conditioning stimulus [55]. The amplitude (in mV, μV, $H_{MAX}/M_{MAX}$, recorded during rest or voluntary contraction) was extracted to determine the effect of resistance training on H-reflex and V-wave amplitudes post training compared to a control group. 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, raw data (means and SD) were derived or calculated from SE, 95% confidence intervals (CI), *P* values, *t* values, or *F* values. Data extraction of all articles was independently assessed for accuracy. Further, when only figures were available in text, data were extracted using Plot Digitizer software [56].

### 2.6 Statistical Analysis

The post-resistance training data from the experimental and control groups for each study were used for the following variables: MEP excitability, silent period duration, CMEP area, $VA_{TMS}$, H-reflex, V-wave, and SICI. 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 SMDs for the main outcome measures [53]. There is now evidence, to suggest that providing estimates of the size of intervention effects, rather than just the existence of effects with *P* values is more valuable. Thus we used SMDs with 95% confidence intervals to measure the intervention effect because the included studies presented outcome measures in a variety of ways. The SMD values of $0.20 \leq 0.49$ indicated small, $0.50 \leq 0.79$ medium, and $\geq 0.80$ large effects [57]. In addition, the results are reported with the SMD, followed by their 95% CI and finally the corresponding *P* value. This approach was taken, because information about the size of effects, rather than just the existence of effects (which only *P* values provide) should be encouraged if the mechanisms by which exercise interventions work are to be determined, or the effects of interventions are to be assessed. For outcome measures in studies that were highly homogeneous, employed the same units of measurement, and had consistent methodological procedures for the electrophysiological recordings, the mean difference (MD) of the changes along with its SD was used to obtain an absolute estimate of effect. In addition, pooled estimates were established via subgroup analysis by testing condition (resting vs. voluntary contraction) for the following electrophysiological outcome measures: MEP amplitude, SICI, H-reflex and V-wave. In order to correct for any bias that was introduced by "double-counting" of subjects in studies that had more than one intervention in the same meta-analyses (i.e., paced resistance training group + self-paced resistance training group), but only one control group, the number of controls in these trials were divided by two [80]. The heterogeneity of the treatment effect between experimental and control groups was evaluated through $I^2$ and the Chi-square test. The $I^2$ statistic, was used to indicate the percentage variance between studies with cut off points corresponding to low (25%), moderate (50%) and high (75%) heterogeneity. In case of heterogeneity exceeding this threshold, a leave-one-out sensitivity analysis was performed to check whether our findings were driven by a single study. All statistical analyses were performed in RevMan 5.3 [54] using an alpha level of $P < 0.05$.

## 3 RESULTS

The PRISMA flow chart (Fig.1) shows the process of study identification, screening and evaluation of the eligibility of included studies. The initial search yielded 3519 titles based upon titles and abstracts. Following the removal of duplicates, the abstracts and titles of the remaining 970 records were screened; 871 were removed for not meeting the inclusion criteria. Ninety-nine full-text papers were assessed for eligibility with a further 58 of these being removed. Additional searches found one additional record, whereupon 42 articles were further screened, with 10 being removed (reasons outlined in Fig. 1), leaving 30 records that entered the meta-analysis. It should be noted that while the Coombs et al. [43] and Leung et al. [40] studies had two independent intervention groups, we counted each study as being only one study each, although the meta-analysis was performed on the studies respective subgroups. The duration of the resistance training interventions ranged from 2-14 weeks with an average training frequency of 2-4 sessions per week.

### 3.1 Quality Assessment

The quality assessment, according to the Downs and Black checklist, is presented in Table 1. This revealed that studies meeting the inclusion criteria ranged between 12 and 23 points (out of a possible 32 points), with a mean score of 17.6 ± 1.9. This indicated a low-to-moderate quality of studies; however, points were not awarded for criteria deemed more relevant to randomized controlled trials and intervention studies, such as blinding of participants, concealment of randomization and statistical power. Most publications were exposed to a high risk of bias for allocation concealment, participant and personnel blinding, and blinding of outcome (Fig. 2).

### 3.2 Changes in Muscular Strength

Complete strength data were extracted from 30 studies that measured maximum strength post-resistance training ($n$ = 325) compared to a control ($n$ = 298). The pooled data indicated that following chronic resistance training, muscular strength increased (SMD 0.67; 95% CI 0.41, 0.94; $n$ = 325; $P < 0.001$), with the heterogeneity of results between the studies being moderate ($Tau^2 = 0.33$; $Chi^2 = 73.89$; $df = 31$; $P < 0.001$; $I^2 = 58\%$; Fig. 3). In most cases, the assessment of strength post training was consistent (task specific) to the type of resistance training employed. However, studies by Carroll et al. [10], Gruber et al. [73], Lee et al. [13] and Nuzzo et al. [11] used isometric testing of muscle strength following either isotonic or ballistic resistance training and hence assessed a non-specific task.

### 3.3 Changes in Corticospinal Excitability

Changes in corticospinal excitability were extracted from 19 studies ($n$ = 202) that assessed MEP amplitude post-resistance training compared to a control ($n$ = 183). The data were separated in to MEPs measured at rest and

during voluntary contraction. The pooled data indicated that resistance training had no effect on MEP amplitude when recorded at rest (SMD 0.49; 95% CI -0.68, 1.66; $P$ = 0.41; 5 studies; $n$ = 114), with the heterogeneity of results between the studies being significant ($Tau^2$= 0.33; $Chi^2$= 73.89; $df$ = 4; $P$ < 0.001; $I^2$ = 87%). However, MEP amplitude was increased by resistance training when recorded during voluntary contraction (SMD 0.55; 95% CI 0.27, 0.84; $P$ < 0.001; 14 studies; $n$ = 271; Fig. 4), with low heterogeneity ($Tau^2$= 0.06; $Chi^2$= 18.26; $df$ = 15; $P$ = 0.25; $I^2$ = 18%).

### 3.4 Changes in Silent Period Duration

Changes in corticospinal inhibition were extracted from 7 studies ($n$ = 96) that assessed the duration of the silent period post-resistance training compared to a control ($n$ = 88). The pooled data indicated that resistance training reduced the silent period (SMD 0.65; 95% CI 0.29, 1.01; $P$ < 0.001; $n$ = 184; Fig. 5) with low heterogeneity across studies ($Tau^2$= 0.06; $Chi^2$= 8.86; $df$ = 7; $P$ = 0.26; $I^2$ = 21%).

### 3.5 Changes in SICI

Changes in SICI were extracted from 7 studies ($n$ = 85) that assessed post-resistance training compared to a control ($n$ = 69). These data were separated into SICI measured at rest and during voluntary contraction. The pooled data indicated that resistance training had no effect on reducing SICI at rest (SMD 0.26; 95% CI -0.21, 0.81; $P$ = 0.35; 2 studies; $n$ = 52), with low heterogeneity ($Tau^2$= 0.00; $Chi^2$= 0.59; $df$ = 1, $P$ = 0.44, $I^2$ = 0%). However, SICI was reduced following resistance training when recorded during voluntary contraction (SMD 0.68; CI 0.14, 1.23; $P$ = 0.01; 5 studies, $n$ = 102; Fig. 6), with moderate heterogeneity ($Tau^2$= 0.20; $Chi^2$= 9.48; $df$ = 6; $P$ = 0.15; $I^2$ = 37%).

### 3.6 Changes in CMEP Area

One study ($n$ = 21) assessed the effects of resistance training on CMEP area, and the results showed cervicomedullary excitability remained unchanged (MD 0.40; $n$ = 21).

### 3.7 Changes in H-reflex Amplitude

Changes in H-reflex were extracted from 10 studies ($n$ = 103) that assessed the amplitude of H-reflexes post-resistance training compared to a control ($n$ =96). The pooled data indicated that resistance training had no effect on the amplitude of resting H-reflexes (SMD 0.16; 95% CI -0.36, 0.68; $P$ = 0.56; $I2$ = 0%; 3 studies; $n$ = 57) with extremely low heterogeneity ($Tau^2$= 0.00; $Chi^2$= 0.15; $df$ = 2; $P$ = 0.93; $I^2$ = 0%). Again, H-reflexes recorded during a voluntary contraction were not significant (SMD 0.15; 95% CI -0.18, 0.48; $P$ = 0.38; 7 studies; $n$ = 142; Fig. 7) and displayed low heterogeneity ($Tau^2$= 0.00; $Chi^2$= 2.46; $df$ = 6; $P$ = 0.88; $I^2$ = 0%).

### 3.8 Changes in $VA_{TMS}$

Changes in $VA_{TMS}$ were extracted from 2 studies ($n$ = 22) that assessed voluntary activation post-resistance training compared to a control ($n$ = 22). The pooled data indicated that resistance training had no statistical effect on voluntary activation, however, the pooled estimate was large (MD 1.41; 95% CI -4.37, 7.20; $P$ = 0.63, with the heterogeneity of results between the studies being high ($Tau^2$= 14.49; $Chi^2$= 5.96, $df$ = 1, $P$ = 0.01; $I^2$ = 83%; Fig. 8).

### 3.9 Changes in V-wave Amplitude

Changes in V-wave were extracted from 5 studies ($n$ = 52) that assessed the amplitude of V-wave post-resistance training compared to a control ($n$ = 49). The pooled data indicated that resistance training increased V-wave amplitude (SMD 0.62, 95% CI 0.14, 1.10; $P$ = 0.01; $I^2$ = 26%; $n$ = 101; Fig. 9) and the heterogeneity across studies was low ($Tau^2$= 0.08; $Chi^2$= 5.38; $df$ = 4; $P$ = 0.25; $I^2$ =26%).

## 4 DISCUSSION

This meta-analysis revealed that chronic resistance training, compared to no training, modified both cortical and subcortical motor circuits that collectively act to improve the activation of the motoneurone pool. Resistance training increased corticospinal excitability, reduced corticospinal inhibition and SICI, whilst increasing V-wave amplitude, which collectively act to increase motoneurone activation and underpin the increase in force.

### 4.1 Resistance Training Increases Force Production

A recent meta-analysis [14], pooling strength data from 19 RCTs, reported that chronic resistance training leads to a large pooled effect (SMD 0.84) for increased force production following 2-14 weeks of training. The present meta-analysis pooled data from 30 studies and showed a moderate increase in force production (SMD 0.67) following resistance training. This finding confirms that resistance training of various modes produces a moderate effect for increased force production. The difference in the pooled-effect size of the current meta-analysis is likely due to the original meta-analysis [14] having a high level of bias, caused by not comparing the data to a control group.

The neural mechanisms that underpin increased force production following resistance training are unclear and inconsistent [14]. At a simplistic level, increasing motoneurone output (motor unit recruitment and firing rate) of the trained muscle would increase force production [58, 59]; however, other mechanisms are also likely to

contribute. For example, increased force production following resistance training could be due to increased motor output from the M1, increased spinal motoneurone excitability and reduced inhibition in descending motor pathways [59]. This meta-analysis confirms that there are subtle changes in the level of excitation and inhibition from the M1 to the spinal cord that act to increase motoneurone output, subsequently increasing force production. Certainly, changes in efferent motor output can be achieved through either enhanced excitation or reduced inhibition within cortical motor areas and we have shown that efferent motor output is enhanced, as determined by increases in V-wave amplitude, corticospinal excitability and reduced intracortical inhibition. Further, an enhanced capacity to voluntarily activate the motoneurone pool of the trained muscle, likely contributes to the increase force production, and supports the large effect that we have reported for improved $VA_{TMS}$. It is likely that the increase in force production following resistance training is accompanied by subtle changes in the entire neuroaxis that includes cortical and subcortical mechanisms that increase motoneuronal output. Additionally, there is good evidence to suggest that increases in strength are also attributable to reduced co-activation of antagonists [21, 23]. However, surprisingly, to date there have been no studies that have directly examined the TMS responses of an antagonist muscle following a period of resistance training.

### 4.2 Resistance Training Increases Cortical and Spinal Excitability

Recently, there has been much discussion about characterizing the potential sites of neural adaptation to resistance training, but identifying which elements within the nervous system (cortical or subcortical) that underpin increased force production has been challenging [14, 60, 61]. One potential neural site that has been consistently reported to be implicated in the increase force production following resistance training is the M1 [10, 38]. An important finding, which is in contrast to a previous systematic review [14], was the moderate effect for resistance training to increase corticospinal excitability (MEP amplitude). In fact, the present meta-analysis, which gathered MEP data from 19 RCTs ($n$ = 271), showed a larger increase (SMD 0.55) in corticospinal excitability compared to the previous meta-analysis by Kidgell et al. [14] that reported a small effect (SMD 0.27). The moderate effect for increased corticospinal excitability is a new finding that indicates that both cortical and spinal mechanisms are modulated following resistance training. In addition, it should be noted that resistance training only affected MEPs recorded during voluntary contraction and not during rest. Understanding the effect of resistance training on resting and actively-evoked responses is complicated, simply by the uncertainty of the level of motoneurone excitability in which the TMS stimulus is superimposed. Although, this meta-analysis sheds some light on this effect, the data should still be interpreted with caution because changes in corticospinal activity could be confounded by the excitability of the motoneurone pool [11], despite controlling for EMG following training.

The magnitude of the MEP induced by single-pulse TMS is the most common neural outcome measured in resistance training studies and is often used to infer changes in M1 excitability. In very simple terms, the amplitude of MEPs reflects the whole corticospinal tract, which includes the excitability of the M1 and the efficiency of neural conduction from the M1 to the spinal cord and transmission to the muscles [62]. Although the amplitude of the MEPs represent the net balance between excitatory and inhibitory influences on the corticospinal tract, MEPs cannot be used to differentiate between cortical mechanisms, including those from cortical micro-circuitry,

the motoneurone pool, and spinal mechanisms [63]. Despite these limitations, and considering the pooled effect we have reported for increased V-wave amplitude (SMD 0.62) following resistance training, it seems that the increase in corticospinal excitability is due to both changes in the excitability of the micro-circuitry of the M1 as well as changes in the modulation of spinal inhibitory and excitatory mechanisms. The present analysis suggests the increase in force production could be attributed to both increased cortico-cortical excitability and increased descending volitional drive following different types of resistance training. The important and new finding is that the analysis comprehensively describes a chain of neurological events that account for the neural adaptations to resistance training. Collectively, this suggests that resistance training improves the efficacy of neural transmission along the descending corticospinal tract.

Over the last two decades, discussions on the neural adaptations to resistance training have inevitably included a role for increased neural drive [9, 59]. Often, the amplitude of the V-wave is used to reflect the magnitude of efferent neural drive from motoneurones during maximal voluntary contractions [9]. This meta-analysis gathered V-wave data from 101 participants and showed that chronic resistance training increased V-wave amplitude (SMD 0.62). Overall, it seems that resistance training increased motoneuronal output that is influenced by cortical and spinal adaptation mechanisms. Certainly, increased cortical voluntary activation could be a supraspinal source for increased motoneurone output following resistance training [13]. It seemed that increased force production following resistance training, in part, is due to an enhanced capacity to voluntarily activate the motoneurone pool of the trained muscle. Furthermore, this analysis reported that $VA_{TMS}$ is increased (MD 1.41) following resistance training due to enhanced motor output from the M1. Although not statistically significant, the magnitude of the effect is large and there is now emerging evidence to suggest that providing estimates of the size of intervention effects, rather than just the existence of effects with *P* values, is more clinically valuable [81]. Therefore, our results support the idea that increased motoneurone output is directly influenced by both cortical and subcortical mechanisms. Because the pooled effect for corticospinal excitability and V-wave is larger (and the large effect for $VA_{TMS}$) than for changes in spinal excitability/inhibition, it seems that supraspinal mechanisms play a greater role in motoneurone activation.

Interestingly, resistance training had no effect on increasing the amplitude of the H-reflex recorded at rest or during voluntary contraction of the target muscle. In fact, all of the included studies showed a trivial effect for resistance training increasing the H-reflex, regardless of the condition in which the H-reflex was recorded. Despite this, it might be that the technical issues associated with the H-reflex technique make it difficult for firm conclusions to be drawn. The interpretation that increased H-reflex following resistance training indicates an increase in motoneurone excitability should also be treated with caution. One of the major caveats to the H-reflex as a determinant of motoneurone excitability is the presence of presynaptic inhibition. The technique itself cannot directly measure the level of presynaptic inhibition, thus the mechanism increasing the H-reflex remain unclear. Furthermore, changes in stimulation intensity also affects the amplitude of H-reflexes, thus moving forward, studies need to ensure that some method of normalisation is included, so comparisons across individuals and studies can be made [82].Despite this, the increase in corticospinal excitability and V-wave amplitude suggests that resistance training alters neural excitability that include subtle changes at both supraspinal and spinal levels.

However, moving forward, in order to disentangle cortical mechanisms from subcortical mechanisms, the amplitude of H-reflexes and V-waves should be examined prior to and after single-pulse TMS resistance training studies. A change in these variables following single-pulse TMS and resistance training would provide evidence for changes in spinal excitability/inhibition.

### 4.3 Resistance Training Reduces Inhibition in Descending Drive

Single- and paired-pulse TMS of the M1 can be used to evaluate the excitability of the inhibitory motor network [64]. In particular, when single-pulse TMS is applied during a voluntary contraction, two SEMG responses are recorded: an excitatory MEP, which is then followed by an inhibitory response, the SP. The SP is mediated by $GABA_B$ and indicates a transient interruption in volitional neural drive from the M1 and withdrawal of descending input to the motoneurone pool [64]. Recently, we reported that a reduction in the duration of the SP was an important neural adaptation to resistance training (SMD -0.66) [14, 65]. The present meta-analysis confirms this and shows that the overall pooled effect for reduced SP is moderate (SMD 0.65) and consistent to previous reports (SMD -0.66 and -0.46) [14, 62]; importantly, the current results reported less bias.

The SP primarily originates from the activation of inhibitory interneurones at the level of the M1, but some evidence suggested that the early part of the SP is of spinal origin [66]. Most of this evidence has been derived from H-reflex studies that showed the first 50-80 ms of SP is due to after-hyperpolarization and inhibition of motoneurones via Renshaw cells [67]. However, due to the limitations of the H-reflex (e.g., presynaptic inhibition), recent data showed that the spinal segment of the TMS-evoked SP is considerably longer than previously reported [64]. With this in mind, it seems that resistance training reduced the synaptic efficacy between inhibitory Renshaw cells and motoneurones, which increases motoneuronal output. This line of inquiry is supported by the increased V-wave amplitude.

Resistance training also reduced the excitability of the intrinsic cortico-cortical inhibitory circuits of the M1 via a moderate (SMD 0.68) reduction in SICI. However, the reduction in SICI was only evident following resistance training when SICI was recorded during background muscle activity. How resistance training specifically affects the intracortical inhibitory network is unclear, but it seems, at the very least, resistance training reduced the responsiveness of the intracortical inhibitory neurones located in the cortical representation of the trained muscle, which increased excitatory drive along the corticospinal pathway [68]. Overall, different types of resistance training target neurones within the nervous system that use $GABA_A$ and $GABA_B$, which leads to reduced synaptic efficacy of their synapses onto corticospinal neurones. The pooled estimate for a reduction in SICI is similar to that for a reduction in the duration of the SP following resistance training. Overall, these findings suggest that both cortical and subcortical mechanisms enhance descending neural drive to the trained muscle via a removal of inhibition within the corticospinal tract.

### 4.4 Excitability of Corticospinal Axons Following Resistance Training

Recent evidence has emerged showing that the excitability of corticospinal axons is facilitated following high-force isometric resistance training. Similar to MEPs induced by TMS, CMEPs can be evoked by electrical or magnetic stimulation at the cervicomedullary junction. CMEPs travel along the same axons as MEPs, have strong monosynaptic connections to motoneurones and are not exposed to presynaptic inhibition, like H-reflexes [69]. Therefore, CMEPs can be used to determine the efficacy of corticospinal-motoneuronal synapses, removing the confounding issue of presynaptic inhibition which can be used to determine motoneurone excitability. Recent evidence suggests that CMEPs are facilitated following acute [70] and chronic resistance training [11, 12]; this meta-analysis, which could only include one study [11], found that resistance training has no effect on enhancing the excitability of corticospinal axons (MD 0.40). Therefore, increased force production following resistance training is not due to increased excitability of corticospinal axons. Rather, it seems to involve subtle adaptations at both a cortical level, that involve reduced corticospinal inhibition, and at a spinal level due to increased neural drive. Clearly, more studies that record CMEPs are required.

### 4.5 Limitations

There are several limitations to this meta-analysis that should be taken into consideration. Although the level of bias reported in this meta-analysis is lower than a previous meta-analysis [14], the studies included within this analysis are of low quality and the analysis could have led to an overestimation of the pooled effect for neural changes and changes in strength. Further, most electrophysiological variables displayed a moderate to high level of heterogeneity, suggesting that there is a need to standardise the methods of assessing both force production and neural mechanisms following resistance training. By standardising testing protocols, the results of individual studies should become more homogeneous making conclusions more robust. In addition, the variable electrophysiological responses across the various techniques (e.g., resting MEPs and $VA_{TMS}$) are high and warrant special attention. The heterogeneity within this analysis is likely due to the different strength tasks performed during training (static vs. dynamic, tonic vs. ballistic, eccentric, etc.), the duration of the training intervention and/or different methodological techniques used to determine the neural adaptations to resistance training. Furthermore, both upper- and lower-limb intrinsic muscles (e.g., first dorsal interosseous and tibialis anterior), which are important in fine motor control compared to more proximal upper and lower-limb muscles (biceps brachii and quadriceps), are more suited to force production and are also likely to contribute to the heterogeneity reported. Lastly, TMS-evoked MEPs assessed at rest might differ from adaptations measured during voluntary contraction. In fact, evoked responses tend to change when obtained during voluntary contraction compared to rest [10, 12; 29], a finding supported by this meta-analysis.

Although this analysis has provided new evidence concerning the sites of neural adaptations to resistance training, some variables (CMEPs and $VA_{TMS}$) should be interpreted with caution due to the overall low volume of studies included. There is a need to adopt more diverse TMS analysis techniques which include a ‘suite’ of measurements such as SP, SICI, LICI, ICF and twitch forces. This would provide a comprehensive chain of events that would

detail the corticospinal responses to resistance training. It would also be useful to consider measurements from muscles that contribute to the overall force-generating capacity, such as synergists and antagonists. Such measures are necessary to comprehensively identify how the CNS contributes to force production.

In the cases where moderate estimates were shown (e.g., SICI and SP), these findings should be considered preliminary due to the small number of studies that entered the meta-analysis. The random effects model that was used to compare the studies because of different methodologies (i.e., type of resistance training, neurophysiological measures performed at rest and during voluntary contraction, different unit of measurement for same variable, etc.), could have underestimated some discrepancies among the included studies. For example, the MEP data used a variety of TMS intensities and some studies used different muscle contraction intensities and different training intensities and frequencies; these differences likely affected the overall estimate obtained. In addition, 13 studies measured the input-output properties of the corticospinal pathway following resistance training, with several studies ($n$ = 11) using the Boltzmann equation. Recent evidence suggests that constructing stimulus-response curves may be a more sensitive measure when examining the effects of a training intervention on corticospinal activity [71]. In particular, examining the area under the recruitment curve (AURC) appears to be superior to using the Boltzmann equation due to poor reliability [71]. Importantly, only two included studies [40-41] examined the AURC and they showed a moderate to large effect (SMD range 0.88-1.56). Thus, there is a need to assess the AURC following resistance training interventions.

This meta-analysis was unable to determine a mechanistic link to the changes in force production following resistance training. In fact, only one study to date has shown a relationship between reduced cortical inhibition and the increase in force production [44]. Although the relationships between electrophysiological measures (such as TMS) are more complex than the expected linear association, there is a need to determine how these subtle changes in the nervous system relate to increased force production. One approach would be to use electrophysiological techniques under the same experimental conditions, as it is likely that the available techniques on their own do not target the same neural elements as those that are activated during resistance training. Therefore, there is a need to standardize the testing protocols to ensure that they match the conditions in which the elements of the nervous system are during both training and testing. Thus, there is need to ensure that the electrophysiological measures match the conditions in which the training was conducted.

## 5 CONCLUSIONS

This is the first systematic review and meta-analysis that provides a quantitative outline of the neural adaptations to resistance training. Overall, the observation suggested that resistance training results in subtle changes in the level of excitation and inhibition derived from a cortical and subcortical level that act to increase motoneurone output and, thereby, strength. Specifically, there are interactions between the GABA-ergic inhibitory circuits that mediate SICI and SP, and this interaction increased motor output by improved efferent drive to the trained muscles. These results confirm that the neural adaptations to resistance training involve both cortical and subcortical adaptations that act to increase motoneurone activation that, at least in part, underpin the training-related increase in muscle strength.

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**Conflicts of Interest**

Ummatul Siddique, Simin Rahman, Ashlyn Frazer, Glyn Howatson, Alan J Pearce and Dawson Kidgell declare that they have no conflicts of interest relevant to the content of this review.

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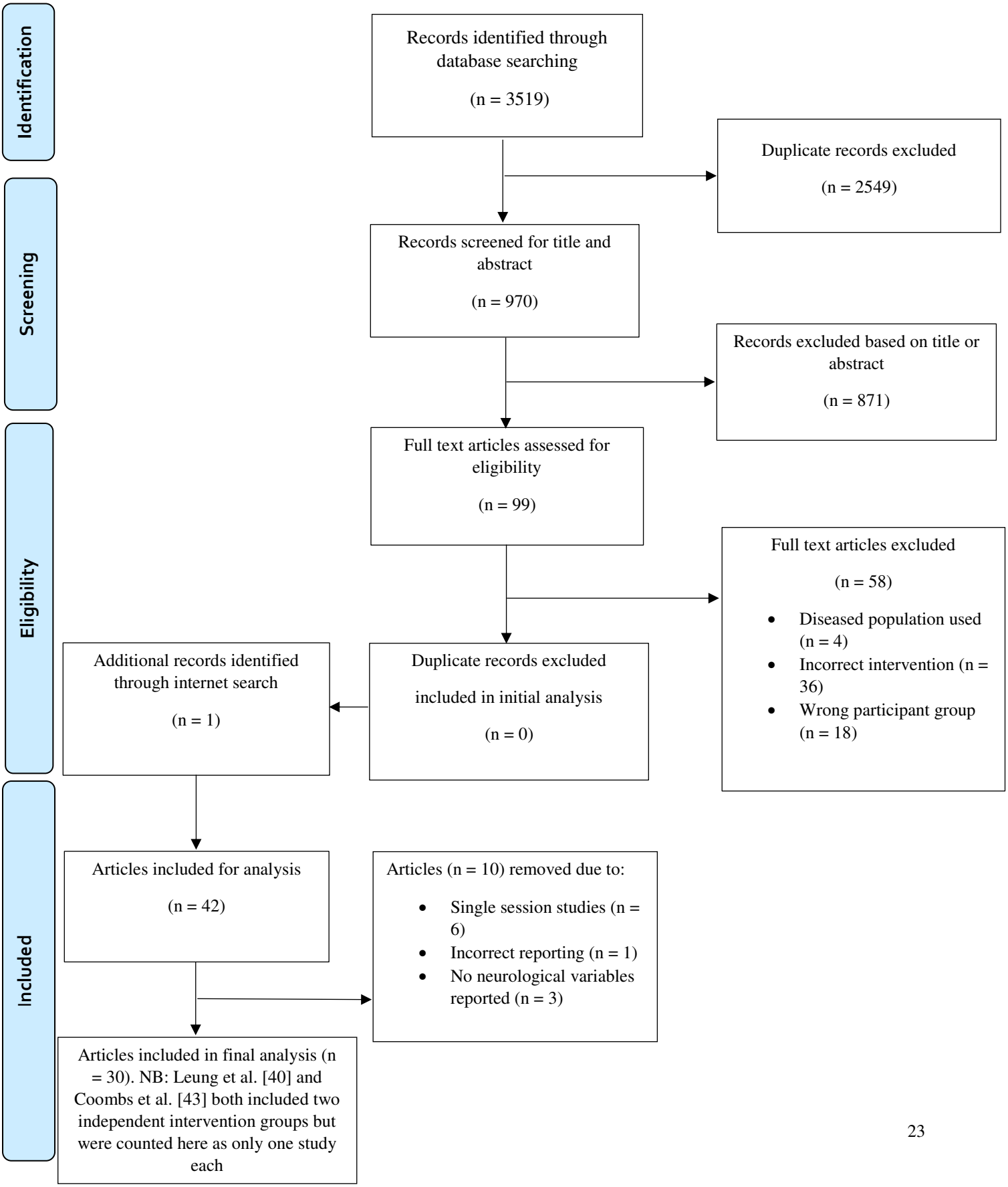




**Figure 1**: PRISMA flowchart of studies included in the review.

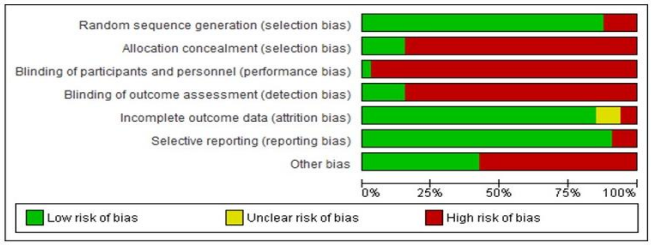


Fig 2. Risk of Bias

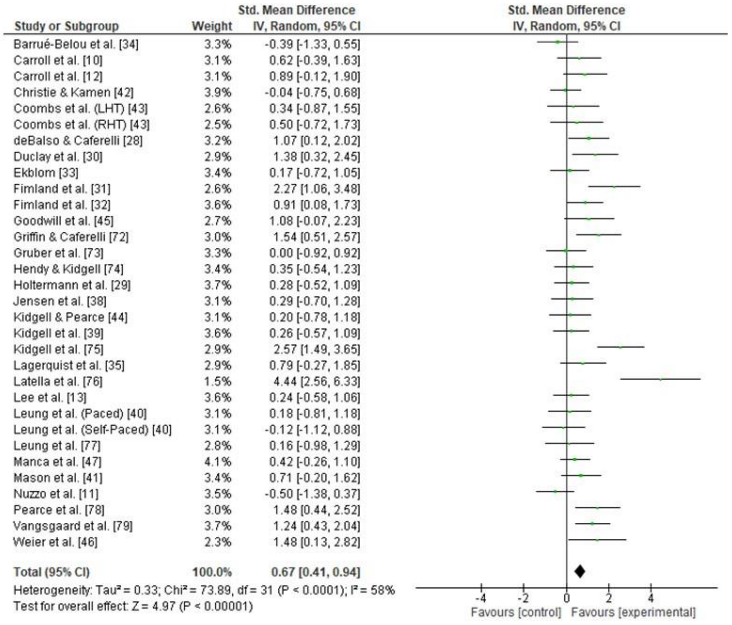


Fig 3. Strength

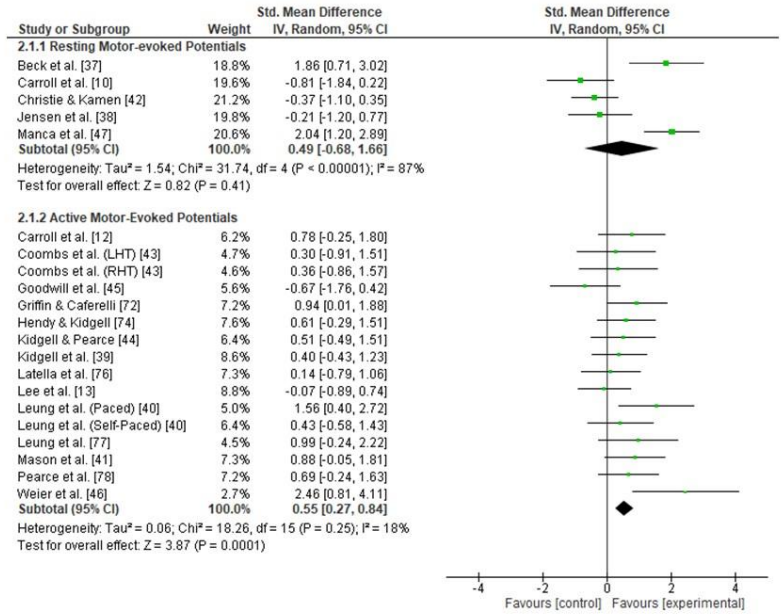


Fig 4. CS excitability

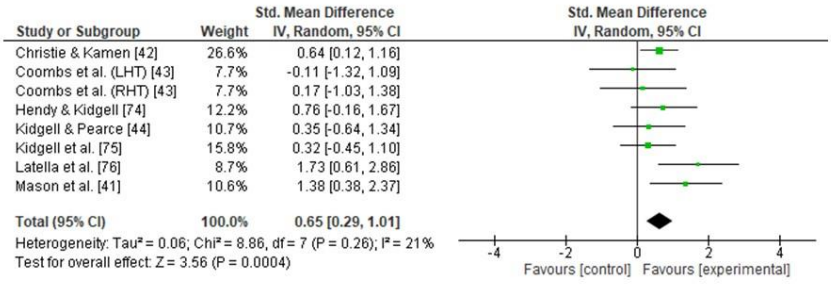


Fig 5. Silent period

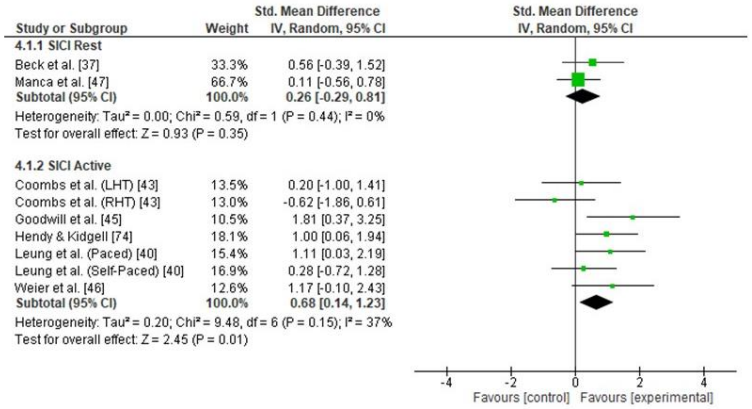


Fig 6. SICI

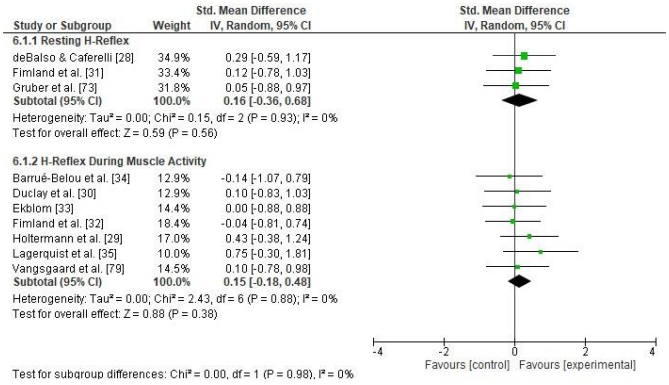


Fig 7 H-reflex

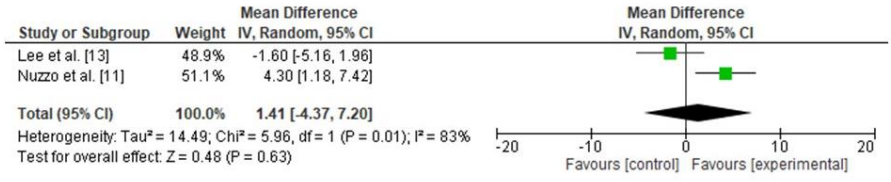


Fig 8. Vol activation

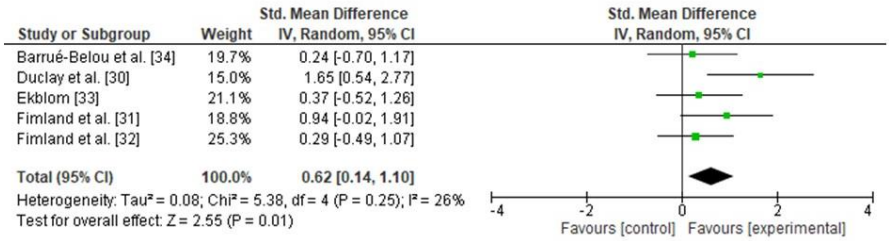
Std. Mean Difference
Study or Subgroup
Weight
IV, Random, 95% CI
Std. Mean Difference
IV, Random, 95% CI
Barrué-Belou et al. [34] 19.7% 0.24 [-0.70, 1.17]
Duclay et al. [30] 15.0% 1.65 [0.54, 2.77]
Ekblom [33] 21.1% 0.37 [-0.52, 1.26]
Fimland et al. [31] 18.8% 0.94 [-0.02, 1.91]
Fimland et al. [32] 25.3% 0.29 [-0.49, 1.07]
Total (95% CI) 100.0% 0.62 [0.14, 1.10]
Heterogeneity: Tau² = 0.08; Chi² = 5.38, df = 4 (P = 0.25); I² = 26%
Test for overall effect: Z = 2.55 (P = 0.01)
-4
-2
0
2
4
Favours [control]
Favours [experimental]

Fig 9. V-wave