Tracking the corticospinal responses to strength training

Joel Mason[1], Ashlyn K Frazer[1], Janne Avela[2], Alan Pearce[3], Glyn Howatson[4,5] and Dawson J Kidgell, PhD[1]

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

[2]Faculty of Sport and Health Sciences, Neuromuscular Research Center, University of Jyväskylä, Jyväskylä, Finland.

[3]Colleg of Science, Health and Engineering, School of Allied Health, La Trobe University, Melbourne, 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

***Corresponding author:**

Dr Dawson J Kidgell, PhD

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

Email: dawson.kidgell@monash.edu

Abstract

Purpose: The motor cortex (M1) appears to be a primary site of adaptation following both a single session, and repeated strength-training sessions across multiple weeks. Given that a single session of strength-training is sufficient to induce modification at the level of the M1 and corticospinal tract, this study sought to determine how these acute changes in M1 and corticospinal tract might accumulate across the course of a two-week heavy-load strength-training program.

Methods: Transcranial magnetic stimulation (TMS) was used to infer corticospinal excitability (CSE), intracortical facilitation (ICF), short and long-interval intracortical inhibition (SICI and LICI) and silent period duration prior to and following each training session during a two-week heavy-load strength-training period.

Results: Following two-weeks of strength-training, increases in strength (15.5%, $P = 0.01$) were accompanied by an increase in CSE (44%, $P = 0.006$) and reductions in both silent period duration (14%, $P < 0.0001$) and SICI (35%, $P = 0.0004$). Early training sessions acutely increased CSE and ICF, and acutely reduced silent period duration and SICI. However, later training sessions failed to modulate SICI and ICF, with substantial adaptations occurring offline between training sessions. No acute or retained changes in LICI were observed. Co-contraction of antagonists reduced by 36% following two-weeks of strength-training.

Conclusions: Collectively, these results indicate that corticospinal plasticity occurs within and between training sessions throughout a training period in distinct early and later stages that are modulated by separate mechanisms of plasticity. The development of strength is akin to the previously reported changes that occur following motor skill training.

Keywords Corticospinal excitability · Cortical plasticity · Intracortical facilitation · Short-interval cortical inhibition · Silent period · Strength training

ABBREVIATIONS

1-RM: One-repetition maximum
AURC: Area under the recruitment curve
AMT: Active motor threshold
CSE: Corticospinal excitability
CI: Confidence interval
SD: Standard deviation
ECR: Extensor carpi radialis
EMG: Electromyography
FCR: Flexor carpi radialis
GABA: γ-Aminobutyric acid
ICF: Intracortical facilitation
LICI: Long-interval cortical inhibition
MEP: Motor-evoked potential
M_{MAX}: Maximal compound wave
MVIC: Maximal voluntary isometric contraction
M1: Primary motor cortex
rmsEMG: Root-mean-square electromyography
RMT: Resting motor threshold
sEMG: Surface electromyography
SICI: Short-interval cortical inhibition
SP: Silent period
TMS: Transcranial magnetic stimulation
rTMS: Repetitive transcranial magnetic stimulation

Introduction

Adaptations within the central nervous system (CNS) underlie training-induced improvements in motor performance. These adaptations commence as early as a single session of training and continue to change between training sessions, due to neural mechanisms associated with use-dependent cortical plasticity (Dayan and Cohen 2011). Use-dependent plasticity has been well studied in the context of skill acquisition (Mawase et al. 2017; Dayan and Cohen 2011), but is lacking in the context of strength acquisition. The process of acquiring a new motor skill has been linked to functional modifications in the intrinsic micro-circuitry of the primary motor cortex (M1), which include the expansion of motor representations (Monfils et al. 2005), the strengthening of existing (Rioult-Pedotti et al. 1998; Rioult-Pedotti et al. 2000) and the formation of new synapses (Kleim et al. 2004; Taube 2011). Importantly, early improvements in motor skill performance are rapid, and there are distinct mechanisms of cortical plasticity that are associated with the early and late stages of skill acquisition (Karni et al. 1998; Floyer-Lea and Matthews 2005; Dayan and Cohen 2011).

Although not as well examined as the motor learning literature, strength training can lead to rapid and substantial improvements in the ability to produce muscular force (Guizelini et al. 2018; Siddique et al. 2019). Such increases in the force-generating capacity of the trained muscles are accompanied by changes in the excitability of the intrinsic micro-circuitry of the M1 due to use-dependant mechanisms (Siddique et al. 2019). Although the rapid development of muscular strength is thought to occur as a result of changes in the CNS (Folland and Williams 2007; Duchateau and Enoka, 2002; Weier et al. 2012), the time-course, specific locus and mechanism of adaptation are poorly understood (Kidgell et al. 2017). Training-induced adaptations are reported to include reduced co-activation of antagonist muscles (Carolan and Cafarelli 1992), increased motoneurone excitability, revealed by increased H-reflexes and V-waves (Aagard et al. 2002) and alterations in motor unit behaviour (Kamen and Knight 2004; Del Vecchio et al. 2019). Many of these changes are reported to have a supraspinal influence that implicate the role of cortical plasticity in strength development (Siddique et al. 2019).

Over last 30 years, transcranial magnetic stimulation (TMS) has been used as a technique to examine the acute and training-related effects of motor training on cortical plasticity. Single- and paired-pulse TMS can quantify cortical plasticity by inferring corticospinal excitability (CSE) through the measurement of the motor-evoked potential (MEP) and intracortical facilitation (ICF), as well as corticospinal inhibition (via the silent period duration) and intracortical inhibition (short and long-latency intracortical inhibition; SICI and LICI, respectively) (Di Lazzaro and Rothwell 2014). Changes in these TMS-evoked responses are regarded as indicators of cortical plasticity confined to the M1. Experimental evidence showed that strength training performed over three to four weeks either increased CSE (Griffin and Cafarelli 2007; Goodwill et al. 2012; Kidgell et al., 2010; Kidgell et al.,

2011; Weier et al. 2012; Pearce et al. 2013; Leung et al. 2015; Mason et al. 2017), decreased CSE (Carroll et al. 2002; Coombs et al. 2016; Jensen et al. 2005; Lee et al. 2009), and reduced the silent period duration (Kidgell and Pearce 2010; Coombs et al. 2016; Mason et al. 2017; Latella et al. 2012). Although these findings are mixed, a recent systematic review concluded that short-term strength training increases CSE, reduces the duration of the silent period and reduces SICI (Siddique et al. 2019). This suggest that use-dependent adaptations within the M1 support improvements in muscular strength. It is possible that the training-related responses following multiple weeks of strength training are simply the culmination of single training sessions. Hortobágyi et al. (2009) used TMS throughout a four-week strength training program to determine the effect of strength training on M1 plasticity. In this study, after every strength training session, real or sham repetitive transcranial magnetic stimulation (rTMS) was applied over the M1. Interestingly, when the M1 was disrupted via rTMS after each session, cumulative strength gains were diminished (Hortobágyi et al. 2009). Importantly, the diminished gain in strength was associated with reduced M1 plasticity. These data suggests that each individual strength training session plays a critical role in the process of acquiring strength, but also directly associates cortical plasticity with strength gains. Therefore, it is conceivable that a summation of the M1 responses could accrue from each session to the next; ultimately generating improvements in muscle strength.Therefore, the previously unexplored idea of tracking the cortical responses session by session might reveal a more detailed time-course of the neural adaptations to strength training.

Theoretical frameworks for early and late phases of cortical plasticity have been established for the acquisition of motor skills (Dayan and Cohen 2011; Karni et al., 1998; Rosenkranz et al. 2007; Kleim et al. 2006; Floyer-Lea and Matthews 2005), which aid in the appropriate prescription and scheduling of skill-based training. However, no such frameworks are available for strength training. The establishment of similar frameworks identifying the cortical responses that shape the acquisition and consolidation of muscular strength would allow practitioners to prescribe training that directly and appropriately targets these underlying mechanisms in order to maintain and improve human health and performance. Therefore, the primary aim of this study was to track the progressive M1 responses prior to and following every strength-training session throughout a two-week strength-training period. It was hypothesised that as strength would increase throughout the training period, the acute excitatory and inhibitory responses (CSE, ICF, silent period, SICI and LICI) would accumulate within each session, leading to changes in M1 plasticity due mechanisms associated with use-dependent plasticity.

Methods

Study Design and Participants

Participants were randomly allocated to a control or experimental group that completed supervised heavy-load strength training of the wrist flexors, three times per week for two-weeks (Figure 1). All

participants provided written informed consent prior to participation. Eighteen healthy individuals (8 female, 10 male, aged 23.45 ± 4.2) were selected on a voluntary basis and all experiments were conducted according to the standards established by the Declaration of Helsinki, and the project was approved by the Monash University Human Research Ethics Committee (MUHREC 11882). All participants were right handed according to the Edinburgh Handiness Inventory (Oldfield 1971) with a laterality quotient >85, were free from peripheral and neurological impairment, and had not participated in strength training for a period of twelve months prior to the commencement of the study. All participants were recruited from the University population and were required to complete an adult safety-screening questionnaire to determine their suitability for TMS (Keel et al. 2011).

Experimental approach

Participants attended a familiarisation session one-week prior to the commencement of baseline testing that involved one-repetition maximum strength testing (1-RM) of the wrist flexors, exposure to single-pulse and paired-pulse TMS, and peripheral nerve stimulation. Following randomisation, participants were allocated to either a strength-training group or a non-training control group. The experimental condition involved heavy-load isotonic strength-training of the right wrist flexors (dominant limb) six times over the course of two weeks, with at least 48 hours rest in between training sessions. Prior to and sixty seconds immediately after the cessation of each strength-training session, measures of motor cortical and corticospinal responses using TMS were obtained. A retention session including all assessments was completed ~72 hours following the completion of the training intervention, and strength measurements were taken at baseline, following one week of training and following two weeks of training. The control group followed an identical protocol to the strength-training group, including frequency and volume of visits to the laboratory, pre- and post-session TMS testing, a retention session and strength testing. However, instead of heavy-load strength training, the control group sat quietly at rest for fifteen minutes.

Voluntary strength testing

Participants performed a standard unilateral one-repetition maximum (1-RM) strength test for the right wrist flexor at baseline, after three training sessions and following six training sessions and at retention (72 h following the sixth training session). Participants were seated in the isokinetic dynamometer, shoulders relaxed and elbow flexed at 90 degrees, with the forearm supinated and fastened firmly on the arm rest. The dynamometer attachment was removed and a weighted dumbbell was used to allow for a more sensitive and functional measure of dynamic strength. The wrist was positioned such that the styloid process sat just beyond the edge of the arm rest, and the relaxed hand hung free. The researcher placed the dumbbell in each participant's hand and instructed them to grasp the dumbbell and completely flex the wrist, moving the hand upward. The exact same procedures were used for TMS

positions, the strength training protocol, and for strength testing of the ECR, however, the forearm was pronated in the case of the latter. Following a warm-up, participants were asked what they considered their 1-RM to be, and this weight served as the starting point for 1-RM establishment. If the trial was successful, the weight of the dumbbell was increased accordingly (0.25-0.5 kg increments). This procedure continued until the subject could no longer complete one repetition, and their prior successful trial served as their 1-RM wrist flexor and extensor strength (Kidgell et al. 2011) and was subsequently used to calculate the intensity for subsequent training. Following each trial, subjects were given 3-mins recovery to minimise the development of muscular fatigue (Kidgell et al. 2011), and typically needed three to five trials to achieve their 1-RM strength.

Strength training protocol

Participants performed supervised, loaded unilateral wrist flexion and extension through 20 degrees, with 0 degrees being the anatomical position, of the dominant arm monitored by a metronome (2 s concentric; 4 s eccentric; Kidgell et al. 2011) and electromagnetic goniometer (ADInstruments, Bella Vista, Australia). Participants completed four sets of 6-8 repetitions at 80% of their 1-RM, with 2.5 min rest between sets. The principle of progressive overload was employed throughout the training period to maximise the training response. Specifically, when participants could complete four sets of eight repetitions, at the beginning of the next training session, the training weight (kg) was increased by 0.5kg. Control participants sat quietly at rest for 15 minutes, matching the time for strength-training completion in the intervention group.

Surface electromyography (sEMG)

The area of electrode placement was shaven to remove fine hair, rubbed with an abrasive skin gel to remove dead skin, and then cleaned with 70% isopropyl alcohol. Surface electromyography (sEMG) was recorded from the right flexor carpi radialis (FCR) muscle using bipolar Ag-AgCl electrodes. As described by Selveanayagam et al. (2011) the electrodes for the FCR were positioned 9 cm from the medial epicondyle of the humerus with an inter-electrode distance (center to center) of 2 cm. As antagonist co-activation data was also collected, extensor carpi radialis (ECR) electrodes were positioned at 45% of the distance from the medial epicondyle of the humerus to the radial styloid process with an inter-electrode distance of 2 cm. A grounding strap was placed around the wrist as the common reference point for all electrodes. sEMG signals were amplified (× 1,000), band pass filtered (high pass at 13 Hz, low pass at 1,000 HZ), digitized online at 2 kHz, recorded (1 s), and analyzed using Power Lab 4/35 (ADInstruments, Bella Vista, Australia). The sEMG was used to record the test and conditioned MEPs obtained during TMS prior to and following each training session throughout the two-week period and at retention 72 h following the intervention. sEMG was also used during the strength-training bout to provide an estimation of antagonist co-contraction.

Transcranial magnetic stimulation

During each testing session, TMS was delivered using two Magstim 200^2 stimulators (Magstim Co., UK) to produce motor evoked potentials (MEPs) in the active FCR via a figure-8 coil. The motor hotspot for the FCR (with posterior-to-anterior-induced current flow in the cortex) was determined and resting motor threshold (RMT) and active motor threshold (AMT) were then established as the stimulus intensity at which at least five of ten stimuli produced MEP amplitudes of greater than 50 μV for RMT and greater than 200 μV for AMT (Rossini et al. 1999). Prior to and following each session throughout the strength-training intervention, AMT and RMT were retested and adjusted if required. To ensure that all stimuli were delivered to the optimal motor hotspots throughout testing, participants wore a tight-fitting cap marked with a latitude–longitude matrix, positioned with reference to the nasion–inion and interaural lines.

All single- and paired-pulse stimuli were delivered during a low-level isometric contraction of the right FCR. Participants were required to maintain a wrist joint angle of 20° wrist flexion in a position of supination. Joint angle was measured with an electromagnetic goniometer (ADInstruments, Bella Vista, Australia), with visual feedback provided on a screen visible to both the participant and the researcher (Hendy and Kidgell 2013). Holding the hand in this joint position equated to 5 ± 1% of the maximal root-mean squared electromyography (rmsEMG). Because this position resulted in a low level of muscle activity, and to ensure that background muscle activity was consistent between TMS stimuli, rmsEMG was recorded 100 ms before the delivery of each TMS pulse. During the TMS trials, visual feedback was presented to the volunteer to display an upper limit of 5% rmsEMG; participants were instructed to maintain their muscle activation levels below this upper limit. The stimulus delivery software (LabChart 8 software, ADInstruments, Bella Vista, NSW, Australia) was set so that stimuli were not delivered if the rmsEMG value, 100 ms immediately prior to the stimulus, exceeded 5 ± 1% (Table 1).

Recruitment curves for the FCR were constructed to determine CSE (MEP amplitude) and silent period duration before and after each heavy-load strength-training bout. For a single stimulus-response curve, 10 stimuli were delivered at 130, 150 and 170% of AMT during a low-level isometric contraction of the FCR. Recruitment curves were also collected for the control group prior to and following 15 minutes of quiet sitting. This was repeated for each strength training session and at retention 72 h after the sixth training session.

To quantify short-interval intracortical inhibition (SICI), 10 single-pulse stimuli and 10 short-interval paired-pulse stimuli were delivered in a random order. The stimulator output intensity was set at 120% AMT, which was determined during familiarization and adjusted if there was a change following each strength training session. The conditioning stimulus for paired-pulse stimulation was set at 80% AMT,

the inter-stimulus interval was 3 ms, and subsequent posterior to anterior current flow was used. To quantify intracortical facilitation (ICF), 10 single-pulse stimuli and 10 paired-pulse stimuli were delivered in a random order. The stimulator output intensity was set at 120% AMT and the inter-stimulus interval was adjusted to 10 ms. Long-interval intracortical inhibition (LICI) was determined by a conditioning stimulus of 120% AMT followed by a test stimulus at 120% AMT with an inter-stimulus interval of 100 ms.

Maximal compound muscle action potential

Direct muscle responses were obtained from the FCR muscle by supramaximal electrical stimulation (pulse width 200 μs) of the Brachial plexus (Erbs point) during light background muscle activity (DS7A, Digitimer, UK). An increase in current strength was applied to Erbs point until there was no further increase observed in the amplitude of the EMG response (M_{MAX}). To ensure maximal responses, the current was increased an additional 20% and the average M_{MAX} was obtained from five stimuli, with a period of 6-9 s separating each stimulus. M_{MAX} was recorded at baseline, prior to and following each training session and then at retention 72 h following the intervention to ensure that there were no changes in peripheral muscle excitability that could influence MEP amplitude.

Data analysis:

Pre-stimulus rmsEMG activity was determined in the FCR muscle 100 ms before each TMS stimulus during pre- and post-testing. Trials were discarded when the pre-stimulus rmsEMG was greater than 5 ± 1% of maximal rmsEMG and then the trial was repeated. The peak-to-peak amplitude of MEPs was measured in the dominant right FCR muscle. MEPs were analyzed (LabChart 8 software; AD Instruments) after each stimulus and flagged automatically with a cursor, providing peak-to-peak values in mV, averaged and normalized to the M_{MAX}, and multiplied by 100. The total area under the recruitment curve (AURC) was calculated via the method of trapezoidal integration using the actual data collected during the construction of corticospinal excitability (MEP amplitude) and corticospinal inhibition (silent period duration) recruitment curves for the FCR before and after every strength-training session. The experimenter was blinded to each condition during all AURC analyses. Silent period durations were obtained from single-pulse stimuli delivered during the construction of the recruitment curve (130–170% AMT) and silent period durations were determined by examining the duration between the onset of the MEP and the resolution of background sEMG, which was visually inspected and manually cursored. The average from 10 stimuli was used to determine silent period durations. SICI and ICF were expressed as a percentage of the unconditioned single-pulse MEP amplitude, while LICI was calculated and expressed as a percentage of the test to conditioning MEP amplitude for each individual paired stimuli. In regards to the changes in SICI, when the SICI percentage change increased following the strength-training sessions and the two-week intervention, this signified a decrease in cortical inhibition and when the SICI percentage change decreased

following training this signified an increase in cortical inhibition. The same percentage changes also applied to LICI.

The extent of co-activation of antagonists was determined by calculating the percentage of the maximal ECR and FCR rmsEMG recorded during wrist flexion 1-RM strength testing, compared to the maximal ECR rmsEMG recording during wrist extension 1-RM testing.

$$\text{Co-activation} = (\text{ECR}/\text{ECR}_{MAX})/\text{ECR}/\text{FCR}) \times 100$$

Peak rmsEMG of the ECR was recorded during wrist extension 1-RM testing; the peak rmsEMG for the ECR was also recorded during wrist flexion 1-RM testing. In a similar manner, peak rmsEMG for the FCR was recorded during wrist flexion 1-RM tests; and during wrist extension testing. For all testing conditions, the rmsEMG max was obtained during the 1-RM tests and was calculated from a 1 s segment that occurred during the peak of the surface EMG trace. The $\text{ECR}/\text{ECR}_{MAX}$ ratio, expressed as a percentage of total activation was then used to correctly interpret the extent of ECR/FCR ratio.

Statistical analysis

All data were screened with Shapiro– Wilk and Kolmogorov–Smirnov tests and were found to be normally distributed (all $P > 0.05$). A 2 × 7 repeated measures analysis of variance (ANOVA) with factors CONDITION (Control and Training) and TIME (Pre, post session 1, post session 2, post session 3, post session 4, post session 5, post session 6 and post session 7) were used to compare changes in pre-stimulus rmsEMG, M-waves, CSE, ICF, silent period, SICI and LICI between conditions and across time. In order to determine the effect of strength training on dynamic muscle strength, a two-way ANOVA was used to compare group (trained vs. control) by week (week 1 vs. week 2) on the pooled changes in strength. For all ANOVAs, if significant main effects were found, a Bonferroni post hoc test was used to analyze the percentage change comparing condition interaction (Control and Training) by time. For all comparisons, effect sizes (ES) of 0.2, 0.5, and 0.8 were established to indicate small, moderate, and large comparative effects (Cohen's *d*), respectively. Prism 8 for Windows (GraphPad Software Inc, La Jolla, CA, USA) was used for all statistical analyses, with the level of significance set as $P < 0.05$ for all testing. All data are presented as mean ± 95% CI in text, whilst mean ± SD is presented in Tables and Figures.

Results

Pre-stimulus rmsEMG, maximal compound waves and motor thresholds

Pooled weekly summary data for measures of electrophysiology is reported in Table 1. In summary, there were no significant differences between groups in M-waves, pre-stimulus rmsEMG, RMT or AMT at baseline and no main effects for TIME or TIME × CONDITION interactions in any measure (All $P > 0.05$; Table 1). Thus, in both the strength-training and control group, there were no changes in

any of the aforementioned measures within any single session during the training program. Further, no changes were observed compared to baseline 72 h following the cessation of the training period in both the strength-training and control group (All $P > 0.05$; Table 1).

Changes in Muscle Strength

The percentage change in the dominant trained wrist flexor following strength-training or no training (control) is presented in Figure 2. Following strength training, there was a main effect for TIME [($F_{2, 32} = 32.7$, $P < 0.0001$] and a GROUP × TIME interaction [($F_{2, 32} = 20.5$, $P < 0.0001$). Post hoc analysis revealed by the end of the first week of strength-training, the strength-training group increased their 1-RM strength of the wrist flexor by 6.3 ± 4.5% (CI -9.80 to -0.0995, $P = 0.04$, $d = 1.24$) compared to a 1.4 ± 3.5% increase in the control group (Table 1). Post hoc analysis also showed after two-weeks of strength-training, the strength-training group increased their 1-RM strength by 15.5 ± 7.6% (CI -18.5 to -8.76, $P < 0.001$, $d = 2.20$) compared to a 1.8 ± 3.5% increase in the control group.

INSERT FIGURE 2

TMS Measurements

The primary aim of the TMS measurements were to investigate both the short-term and long-term adaptations to strength-training. Because none of the control group measurements showed any significant changes across testing sessions or training weeks (i.e., within group main effects, see Table 2), the data presented in the short-term and long term responses to strength-training only include the main interaction effects between the strength-training and control groups.

Short-term MEP responses to strength training: Figure 3A illustrates the percentage change following each strength-training session across the two-week intervention for the strength-training group only. There was a significant main effect for increased CSE following the first session (CI -93.1 to -22.9, $P < 0.001$, $d = 1.82$), second session (CI -91.8 to -21.5, $P > 0.001$, $d = 1.89$), third session (CI -77.3 to -7.11, $P = 0.008$, $d = 1.17$), fourth session (CI -79.8 to -9.58, $P = 0.004$, $d = 1.68$), fifth session (CI -81.9 to -11.7, $P = 0.002$, $d = 1.42$), sixth session (CI -80.0 to -9.77, $P = 0.004$, $d = 1.45$) and 72 h after the last strength training session [session 7, retention] (CI -78.3 to -8.10, $P = 0.006$, $d = 2.12$) compared to the control group. There were no differences in CSE between sessions for the strength-training group, thus the short-term effects of training seemed to be largest in response to the first training session and then sustained across subsequent training sessions (Figure 3A).

Longer-term MEP responses to strength training: The longer-term adaptations to training are defined as the differences that occur when comparing the pre-training values obtained in the baseline test, the one-week test (session 3), the two-week test (session 6) and the retention test (session 7). These

responses are illustrated in Figure 3B. For the strength-training group, AURC for CSE increased by 53 ± 43% (CI 35.7 to 68.9, $P < 0.0001$, d=1.67) compared to the 0.5 ± 4.5% increase in the control group at the end of training week 1, and by 45 ± 39% (CI 30.4 to 60.5, $P < 0.001$, d=1.60) compared to the 0.2 ± 2.6% increase in the control group at the end of training week 2. The AURC for CSE was also increased from baseline 72 h following the strength-training intervention by 44 ± 27% (CI 23.6 to 62.8, $P < 0.001$, d=2.13) compared to the control group (Figure 3B).

INSERT FIGURE 3A-B

Short-term corticospinal inhibitory responses to strength training: Figure 4A illustrates the percentage change in silent period following each strength-training session across the two-week intervention for the strength-training group compared to the control group. In the strength-training group, there was a main effect for reduced silent period duration following the first session (CI 8.26 to 20.3, $P < 0.001$, $d = 2.18$), second session (CI 7.74 to 19.8, $P < 0.001$, $d = 2.77$), third session (CI 4.92 to 17.0, $P < 0.001$, $d = 1.73$), fourth session (CI 1.82 to 13.9, $P = 0.002$, $d = 1.72$), fifth session (CI -2.59 to 14.7, $P = 0.0004$, $d = 2.46$), sixth session (CI 1.73 to 13.8, $P = 0.002$, $d = 2.35$) and 72 h after the last strength-training session (CI 8.25 to 20.3, $P < 0.001$, $d = 1.96$) compared to the control group. There was a significant difference in the duration of the silent period between session 1 and session 4 (CI -12.5 to -0.402, $P = 0.025$, $d = 0.92$) and session 1 and session 6 (CI -12.6 to -0.493, $P = 0.021$, $d = 1.20$) for the strength-training group. Corticospinal inhibition appears to reduce rapidly following the first training session and then steadily return towards baseline across subsequent strength-training sessions (Figure 4A).

Longer-term corticospinal inhibitory responses to strength training: The longer-term adaptations to training are defined as the differences that occur when comparing the pre training values obtained in the baseline test, the one-week test, the two-week test and the retention test. These responses are illustrated in Figure 4B. For the strength-training group, AURC for silent period reduced by 13 ± 6.3% (CI 6.69 to 19.6, $P < 0.001$, $d = 2.56$) compared to the 0.1 ± 2.5% increase in the control group at the end of training week 1 and reduced by 8% ± 3.9% (CI 2.77 to 15.6, $P < 0.002$, $d = 2.26$) compared to the 1.1 ± 1.3% increase in the control group at the end of training week 2. The AURC for corticospinal inhibition also reduced 72 h following the strength-training intervention by 14 ± 10% (CI 9.33 to 22.2, $P < 0.001$, d =1.58, Figure 4B) compared to the control group.

INSERT FIGURE 4A-B

Short-term SICI responses to strength training: Figure 5A illustrates the percentage change in SICI following each strength-training session across the two-week intervention for the strength-training

group. In the strength-training group, there was a main effect for a release in SICI following the first session (CI -56.3 to -10.9, $P = 0.002$, $d = 1.33$), second session (CI -60.0 to -14.6, $P < 0.001$, $d = 1.43$), third session (CI -50.7 to -5.33, $P < 0.003$, $d = 1.55$), and 72 h after the last strength-training session (CI -58.3 to -13.0, $P < 0.001$, $d = 1.56$) compared to the control group. Interestingly, there were no differences in SICI release across strength-training sessions four, five and six for the strength-training group (all $P > 0.05$, Figure 5A).

Longer-term SICI responses to strength training: Again, the longer-term adaptations to training are defined as the differences that occur when comparing the pre-training values obtained in the baseline test, the one-week test, the two-week test and the retention test. These responses are illustrated in Figure 5B. For the strength-training group, SICI reduced by 33 ± 25% (CI -52.6 to -12.5, $P < 0.001$, $d = 1.68$) compared to the 0.4 ± 7.6% increase in the control group at the end of training week 1. There were no differences in SICI release between the strength-training group and the control group at the end of week 2 (CI -35.8 to 4.29, $P = 0.163$, $d = 2.26$), despite a large effect. However, SICI was reduced for the strength-training group at 72 h following the strength-training intervention by 35 ± 25% (CI -54.7 to -14.6, $P < 0.001$, $d = 1.51$) compared to the control group.

INSERT FIGURE 5A-B

Short-term and longer-term ICF responses to strength training:

Figure 6A illustrates the percentage change in ICF following each strength-training session across the two-week intervention for the strength-training group. In the strength-training group, there was a main effect for increased ICF following the first session (CI -27.8 to -3.66, $P = 0.001$, $d = 1.48$) and second session (CI -25.2 to -0.231, $P < 0.04$, $d = 1.38$), compared to the control group. ICF also increased for the strength-training group following the fourth session (-24.5 to -0.396, $P < 0.036$, $d = 0.72$), but the magnitude of this change was not different to the control group. There were no differences in ICF across strength-training sessions three, five and six (all $P > 0.05$, Figure 6A) and at retention for the strength-training group compared to the control group. For the strength-training group, ICF increased by 13 ± 10% (CI -23.9 to -4.37, $P = 0.002$, $d = 1.86$) compared to the 1.0 ± 1.8% decrease in the control group at the end of training week 1 and increased by 12 ± 11% (CI -21.4 to -1.21, $P = 0.023$, $d = 1.57$, Figure 6B) compared to the 0.7 ± 1.7% decrease in the control group after the end of training week two. There were no differences in ICF between the strength-training and control groups at retention (CI -17.9 to 3.17, $P = 0.245$).

INSERT FIGURE 6A-B

Short-term and long-term LICI responses to strength training:

In the strength-training group, there were no main effects for a change in LICI from strength-training session 1 to strength-training session 6 ($P = 0.463$) or following week 1 of training ($P > 0.999$), week 2 ($P = 0.993$) or at retention ($P = 0.99$) compared to the control group.

Changes in Co-Activation of Antagonists:

Figure 7 illustrates the antagonist co-activation index obtained during the weekly 1-RM strength testing following week 1 and week 2 for the strength-training and control group. There was a significant main effect for a reduction in antagonist co-activation from week 1 to week 2 compared to the control group (CI -3.08 to -2.30, $P = 0.02$, $d = 1.80$).

INSERT FIGURE 7

Discussion

This study examined the time-course effects of strength-training on the formation of use-dependent cortical plasticity and how it contributed to improvements in muscular strength. The main findings are **1)** increases in strength were apparent after three sessions of strength-training, and further increases were observed following six sessions, **2)** following two-weeks of strength-training, CSE was increased with concurrent decreases in the duration of the silent period and SICI; however, **3)** the acute cortical responses to strength-training did not accumulate within each training session, rather **4)** the substantial and rapid responses to a single session of strength-training were either maintained (CSE), reduced (silent period) or abolished (ICF and SICI) during subsequent sessions, indicating that neural adaptations occurred between training sessions. Further, antagonist co-contraction during training was substantially reduced in week two compared to week one. These findings indicate that the M1 undergoes substantial use-dependent plasticity from the first strength-training session onwards alongside reduced co-contraction of antagonists in order to drive improvements in muscular strength. These adaptations are rapid, and beyond the immediate cellular response to the initial strength-training session (such as increases in synaptic efficacy), occur primarily between strength-training sessions, and culminate in longer-term functional changes (i.e., neurogenesis).

The time-course of strength development

The current study provides insight into the temporal scale of strength improvement, with significant increases in strength following just three strength-training sessions, and further increases following six strength-training sessions. The time-course of strength improvement supports the findings of Griffin

and Cafarelli (2003) who observed strength increases following just two sessions of isometric strength training of the tibialis anterior, and further progressive increases throughout the rest of a four-week strength-training period. There are several lines of evidence suggesting that just one strength-training session can produce increases in strength upwards of 10% (Hood and Forward 1965; Christie and Kamen 2004; Nuzzo et al. 2019), and improvements in strength over a three-day strength-training period can be maintained three months following the cessation of training (Kroll 1963). The magnitude of strength gain following six sessions of training is comparatively large in reference to studies reporting improvements following longer strength-training periods (Ahtianen et al. 2003; Gomes et al. 2018; Serra et al. 2018). The difference is likely due to the subjects recruited in the current study being novices to any form of strength-training. Experimental evidence shows that inexperienced strength trainers obtain larger gains in strength across a multi-week training program when compared with subjects who are more experienced (Ahtianen et al. 2003). Further, discrepancies in the magnitude of strength improvements between studies might also be explained by the elements of the strength-training used in the current study, including heavy-load, dynamic contractions with external pacing (Leung et al. 2017; Kidgell et al. 2010; Mason et al. 2019). In summary, increases in strength begin very early after the onset of strength-training, and accumulate across training weeks, reinforcing the existing evidence that strength-training is an effective stimulus capable of producing rapid, lasting improvements in performance (Siddique et al. 2019).

The training-related corticospinal and M1 responses are similar to the short-term acute responses.

Seventy-two hours following the final session, substantial changes in M1 plasticity were observed when compared to baseline and to the control group, which is consistent with the literature (see Siddique et al. 2019 for review). Similarly, the responses to the initial strength-training session were well-aligned with current evidence (see Mason et al. 2019 for review). With the exception of ICF, the corticospinal and M1 responses (or lack of, see LICI) to the initial strength-training session mirrored the responses measured at the retention period following the two-week strength-training period. The general alignment between the acute responses to the initial strength-training session and the retained responses following two-weeks of strength-training, provides the foundation for a simple and progressive accumulation of neural responses from session one onwards. However, from week one to week two, there appears to be no accumulation in the acute M1 and corticospinal responses to each individual strength training session as hypothesised. Rather, the M1 and corticospinal responses are substantially and rapidly enhanced from the first strength-training session and are maintained (CSE), reduced (silent period) or eventually eliminated (SICI and ICF) across the course of the sixth strength-training session. Combined, these results indicate that substantial neural adaptations between strength-training sessions could be influencing the corticospinal and M1 adaptations supporting the increase in strength throughout a training period.

Identifying the neural mechanisms that accompany strength development

Prior to discussing the mechanisms of cortical plasticity throughout the strength-training period, it may be useful to postulate what purpose cortical plasticity could serve. Alterations in corticospinal output during and following strength-training likely contributed to the development of strength through an influence on motor unit behaviour. The magnitude of muscle activation, and therefore the amount of force produced, is determined by the number of activated motor units (recruitment) and the rate at which the motoneurones are discharged (rate coding), with both being altered following strength-training (Farina et al. 2016). Recent evidence, using validated techniques previously unavailable (Farina et al 2016), indicates that strength gains following four-weeks of isometric strength-training are driven by decreased motor unit recruitment thresholds and increased discharge rates (Del Vecchio et al. 2019). This aligns with earlier evidence whereby increases in strength are due to adaptations in motor unit recruitment and rate coding following isometric strength-training (Duchateau et al. 2006; Van Cutsem et al.1998; Vila-Cha et al. 2010; Kamen and Knight 2004). Given that motor units are controlled by input to the motoneurone pool from the corticospinal tract, alterations in motor unit behaviour likely involve adaptive changes in the corticospinal tract from the M1 to the spinal motoneurone pool. Of these potential sites, adaptations at a supraspinal level are a primary candidate (Siddique et al. 2019; Semmler and Enoka 2000; Schubert et al. 2008). Indeed, Del Vecchio and colleagues (2019) proposed that increased net excitatory synaptic input to the motoneurone pool was the likely mechanism driving motor unit adaptations as opposed to modification to the intrinsic motoneurone properties. This, paired with evidence that strength-training increases voluntary activation with no increase in cervicomedullary excitability (Nuzzo et al., 2017; Siddique et al. 2019), suggests that modulation at the level of the M1 may be responsible for alterations in motor unit behaviour. Therefore, it is conceivable that in the current study, increases in CSE and decreases in inhibitory input to the motoneurone pool generated changes in motor unit recruitment and rate coding throughout the strength-training period, which ultimately underpinned the observed increases in strength. These corticospinal responses likely reflect an improved ability of the M1 to maximally recruit and discharge motor units, which is demonstrated by the increase in the input-output properties of the corticospinal tract following strength-training (i.e. change in AURC for CSE and silent period). However, a potential caveat to this line of inquiry is that there is evidence to suggest that the corticospinal tract is not the only descending motor pathway that provides synaptic input to the spinal motoneurone pool, which could alter motor unit behaviour (Riddle et al. 2009). For example, evidence shows that the reticulospinal tract is associated with force production (Baker and Perez 2017), therefore, it could be the case that the reticulospinal tract was also modulated as a result of the strength-training intervention. It is also likely that modulation in the reticulospinal tract, also contributed to the increase in force, presumably through enhanced direct and indirect synaptic input to the spinal motoneurone pool. The time-course of these adaptations also

supports this notion, as the increase in strength occurred rapidly and directly in line with the timeframes for alterations in motor unit behaviour (i.e. session by session, Christie and Kamen 2004). Further, reduced antagonist co-activation during the second week of strength-training is also consistent with existing evidence demonstrating rapid antagonist alterations following strength-training (Hight et al. 2017). Thus, changes in antagonist behaviour, alongside the agonist corticospinal responses, collectively contribute to increases in strength (Mason et al. 2019).

The timing of cortical plasticity within this study warrants further discussion, as it provides insight into how the rapid cellular responses ultimately develop into longer-lasting functional changes (i.e., synaptogenesis) following two-weeks of strength training. The presence of substantial adaptations between training sessions and the formation of cortical plasticity across the strength-training program add to the consistent comparisons between the development of strength and the acquisition of a motor skill (Leung et al. 2015; Leung et al. 2017; Jensen et al. 2005; Mason et al. 2019). In fact, it seems that strength-training induces neurogenesis that occurs between training sessions. Although there are no strength-training studies that have examined this notion alongside the time-dependent adaptations to strength-training, the use of skill acquisition frameworks may aid in the interpretation of the current result and the notion that strength-training induces neurogenesis.

Diminishing responses to individual sessions and significant adaptations between strength-training sessions may be indicative of early and late phases of cortical plasticity supporting strength acquisition, resembling the distinct early and later phases of skill acquisition identified by imaging, behavioural and TMS studies (Karni et al. 1998; Rosenkranz et al. 2007; Kleim et al. 2006; Floyer-Lea and Matthews 2005). Early responses to skill training are commonly attributed to changes in existing synaptic strength, and later responses attributed to distinct functional processes such as synaptogenesis or neurogensis (Rosenkranz et al. 2007; Kleim et al. 2006). Therefore, the early phase of strength development might also be characterised by changes in existing synaptic efficacy, which may occur both during training and at rest, whereas later changes may reflect structural changes that occur between training sessions. This idea is supported by the acute inhibitory responses to early training sessions, as a reduction in GABA-mediated inhibition is necessary for the early enhancement of synaptic efficacy (Hess et al. 1996; Hess and Donoghue 1994) and is associated with the acquisition of novel motor tasks (Stagg et al. 2011; Floyer-Lea et al. 2006; Butefisch et al., 2000; Kida et al. 2016; Mooney et al. 2019). Further, a lack of acute online inhibitory responses later in training is compatible with evidence that longer-term structural plasticity occurs between training sessions, not within training sessions (Mednick et al. 2011), and that synaptogenesis does not directly contribute to initial acquisition, but occurs later in the learning process underpinning consolidation and retention of a skill (Kleim et al. 2004). However, the role of synaptogenesis and the functional reorganisation of M1 in strength development remains to be determined, despite evidence from animal models that unlike skill training, strength-training is

incapable of inducing changes in motor map representations regardless of training stage (Remple et al. 2001). This is despite evidence of increased volume of excitable synapses onto motoneurones following strength-training (Adkins et al. 2006).

It must be noted in contrast to the skill training literature (Kleim et al. 2006; Rosenkrantz et al. 2007), CSE remained substantially modulated by each strength-training session, despite all other indicators of cortical plasticity diminishing across the strength-training period. An increase in CSE immediately following a single session of strength-training appears to be an important factor for cortical plasticity underpinning strength development, as its abolishment via rTMS following strength-training reduces strength improvements considerably (Hortobágyi et al. 2009). Collectively, this suggested that CSE could contribute to both early cellular and later structural plasticity (i.e. neurogenesis) serving increases in strength, despite a lack of correlation between gains in strength and increased CSE following several weeks of strength-training (Jensen et al. 2005; Mason et al. 2017). The lack of correlation is likely due to other neural structures and systems being involved in strength development, especially the intrinsic spinal circuitry (Siddique et al. 2019). Thus, there is a need to examine multiple sites within the CNS in order to provide a greater understanding of which systems in the CNS are most related to changes in strength. However, CSE is not just an indicator of corticospinal plasticity, it is also thought to increase as a function of fatigue (Mason et al. 2019; Latella et al. 2017), representing a point of difference between strength-training and the typically low-fatiguing paradigms used in skill training. Whilst it is possible that repeated acute modulation of CSE through strength-training is sufficient to trigger mechanisms of structural plasticity (synaptogenesis) between strength-training sessions, conclusions regarding the functional consequences of increased CSE are preliminary in this context (Bestmann and Krakauer 2015).

The current study has a number of limitations that must be considered when interpreting the findings. Firstly, a more precise temporal scale of strength improvements would have been generated through testing strength alongside every TMS testing day. However, this is logistically difficult, given the ability of even one maximum testing session to influence subsequent neuromuscular responses and performance (Nuzzo et al. 2019). Secondly, strength-training studies typically use more precise measurements of strength testing than 1-RM testing, such as maximal isometric voluntary contractions (MVIC) (Kidgell et al. 2017). However, previous strength-training studies have identified using different testing and training apparatus or techniques as a limitation. Indeed, adaptations are typically specific to the training involved (Brownstein et al. 2018), and are therefore better assessed by identical protocols. Additional limitations include a lack of a more comprehensive assessment protocol to assess spinal excitability, such as volitional waves and cervicomedullary evoked potentials. Future studies should seek to track the responses to both skill and strength-training across an entire training period to discern differences. Importantly, beyond the assessment of peripheral excitability, the current study was

unable to determine the contribution of fatigue to the single session responses. Therefore, similar upcoming studies should include techniques (such as cortical voluntary activation) to discern the role of both peripheral and central fatigue in mediating the acute and short-term responses to strength training and, how they relate to the process of acquiring muscular strength.

In summary, this study provides new insight into how the rapid responses to a single bout of strength-training evolve into longer-term cortical plasticity that accompanies the increases in muscle strength following a two-week strength-training period. These results add to the notion that the repeated stimulus of strength-training is sufficient to induce long-lasting changes in muscle strength and cortical plasticity. Combined, the findings provide evidence for early and late phases of strength development, mediated by distinct cortical mechanisms similar to the frameworks observed for the development of motor skills. Importantly, the alterations in CSE and inhibition across the strength-training program occur acutely and between training sessions, conceivably to drive the changes in motor unit behaviour, which ultimately seem responsible, at least in part, for improvements in force production. Understanding the time-course and location of neural adaptation to heavy-load strength-training will allow practitioners to design more efficient training programs to develop and preserve skeletal muscle strength for maintenance of health and improve human performance. Finally, Kleim and Jones (2008) suggested that cortical plasticity underlying improvements in motor skill is perhaps best considered a process rather than a single measureable event, as it involves a cascade of events at the molecular, cellular and structural levels (Kandel 2001). The same must be considered for the adaptations underpinning improvements in strength. Thus, the relationship between corticospinal and M1 plasticity and strength development is an area ripe for further exploration.

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