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Author(s): Akalu, Yonas; Tallent, Jamie; Frazer, Ashlyn K.; Siddique, Ummatul; Rostami, Mohamad; Vallance, Patrick; Howatson, Glyn; Walker, Simon; Kidgell, Dawson J.

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Strength-trained adults demonstrate greater corticoreticular activation versus untrained controls

Yonas Akalu^{1,2} | Jamie Tallent^{1,3} | Ashlyn K. Frazer¹ | Ummatul Siddique¹ |
 Mohamad Rostami¹ | Patrick Vallance¹ | Glyn Howatson^{4,5} |
 Simon Walker⁶ | Dawson J. Kidgell¹ 

¹Monash Exercise Neuroplasticity Research Unit, Department of Physiotherapy, School of Primary and Allied Health Care, Faculty of Medicine, Nursing and Health Science, Monash University, Frankston, Victoria, Australia

²Department of Human Physiology, School of Medicine, University of Gondar, Gondar, Ethiopia

³School of Sport, Rehabilitation and Exercise Sciences, University of Essex, Colchester, UK

⁴Department of Sport, Exercise and Rehabilitation, Faculty of Health and Life Sciences, Northumbria University, Newcastle upon Tyne, UK

⁵Water Research Group, North-West University, Potchefstroom, South Africa

⁶NeuroMuscular Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

Correspondence

Dawson J. Kidgell, Monash Exercise Neuroplasticity Research Unit, Department of Physiotherapy, School of Primary and Allied Health Care, Faculty of Medicine, Nursing and Health Science, Monash University, Moorooduc Hwy, PO Box 527, Frankston, Melbourne, VIC 3199, Australia.
 Email: dawson.kidgell@monash.edu

Abstract

The rapid increase in strength following strength-training involves neural adaptations, however, their specific localisation remains elusive. Prior focus on corticospinal responses prompts this study to explore the understudied cortical/subcortical adaptations, particularly cortico-reticulospinal tract responses, comparing healthy strength-trained adults to untrained peers. Fifteen chronically strength-trained individuals (≥ 2 years of training, mean age: 24 ± 7 years) were compared with 11 age-matched untrained participants (mean age: 26 ± 8 years). Assessments included maximal voluntary force (MVF), corticospinal excitability using transcranial magnetic stimulation (TMS), spinal excitability (cervicomedullary stimulation), voluntary activation (VA) and reticulospinal tract (RST) excitability, utilizing StartReact responses and ipsilateral motor-evoked potentials (iMEPs) for the flexor carpi radialis muscle. Trained participants had higher normalized MVF (6.4 ± 1.1 N/kg) than the untrained participants (4.8 ± 1.3 N/kg) ($p = .003$). Intracortical facilitation was higher in the strength-trained group ($156 \pm 49\%$) ($p = .02$), along with greater VA ($98 \pm 3.2\%$) ($p = .002$). The strength-trained group displayed reduced short-interval-intracortical inhibition ($88 \pm 8.0\%$) compared with the untrained group ($69 \pm 17.5\%$) ($p < .001$). Strength-trained individuals exhibited a greater normalized rate of force development (38.8 ± 10.1 N·s⁻¹/kg) ($p < .009$), greater reticulospinal gain (2.5 ± 1.4) ($p = .02$) and higher ipsilateral-to-contralateral MEP ratios compared with the untrained group ($p = .03$). Strength-trained individuals displayed greater excitability within the intrinsic connections of the primary motor cortex and the RST. These results suggest greater synaptic input from the descending cortico-reticulospinal tract to α -motoneurons in strength-trained individuals, thereby contributing to the observed increase in VA and MVF.

Abbreviations: AMT, active motor threshold; CMEP, cervicomedullary motor-evoked potential; cMEP, contralateral motor-evoked potential; ICF, intracortical facilitation; iMEP, ipsilateral motor-evoked potential; MEP, motor-evoked potential; M_{MAX} , maximum compound wave; MVF, maximum voluntary force; RFD, rate of force development; RST, reticulospinal tract; SICI, short-interval cortical inhibition; TMS, transcranial magnetic stimulation; VA, voluntary activation; VART, visual auditory reaction time; VRT, visual reaction time; VSRT, visual startling reaction time.

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KEYWORDS

reticulospinal tract, StartReact protocol, strength-training, transcranial magnetic stimulation

1 | INTRODUCTION

Strength-training increases muscle strength, the maximum force produced by a muscle (Hong et al., 2014; Moore et al., 2004). Improving muscular strength serves to reduce the likelihood of injury occurrence (Brooks et al., 2006), lowers the probability of encountering musculoskeletal conditions such as osteoarthritis (Zhang & Jordan, 2010), enhances metabolic well-being (Ihalainen et al., 2019), augments the mobility of older adults (Brandon et al., 2003) and improves athletic ability (Comfort et al., 2012). Strength-training is therefore recommended for all populations including athletes and young and older adults (2009; Liu & Latham, 2009).

Neural adaptation underpins an increase in the maximum voluntary force-generating capacity of a muscle following strength-training (Carroll et al., 2002; Jensen et al., 2005; Nuzzo et al., 2017; Siddique et al., 2020). Strength-training is thought to increase neural drive to the trained muscle (Aagaard et al., 2002; Tøien et al., 2018) and this increase in drive or motor command might be a result of strength-training-induced changes at different levels within the central nervous system (CNS) from the primary motor cortex (M1) to the spinal motoneurons. Possible changes include an increase in corticospinal excitability and a decrease in short-interval cortical inhibition (SICI) (Siddique et al., 2020). However, recent studies have reported an absence of change in SICI (Ansdell et al., 2020) or corticospinal excitability (Ansdell et al., 2020; Colomer-Poveda et al., 2021). This implies the probability or presence of other neural structures or descending tracts, possibly the reticulospinal tract (RST), underpinning training-induced strength gain (Aagaard et al., 2020; Atkinson et al., 2022; Hortobágyi et al., 2021).

The RST is a major extrapyramidal tract originating from the pontomedullary reticular formation that descends bilaterally to form direct and indirect synaptic connections with α -motoneurons of proximal and distal muscles (Brownstone & Chopek, 2018; Drew et al., 2004; Nathan et al., 1996). A recent study reported that the RST contributes to the control of contraction force in upper-limb muscles (Glover & Baker, 2022). Other work has supported the idea that the RST could be an underlying mechanism for improved strength following strength-training in non-human primates (Atkinson et al., 2022; Glover & Baker, 2020). The deep anatomical placement of the reticular formation within the brainstem makes it

unfeasible to assess the effectiveness/or excitability of the RST using non-invasive methods in human subjects (Glover & Baker, 2020). However, the StartReact protocol represents an indirect non-invasive approach, to evaluate the efficacy of the RST in humans. This task involves a reaction time paradigm where participants are instructed to respond to a visual cue, presented either in isolation or concurrently with an unforeseen loud or soft auditory stimulus, by executing a pre-determined action (Carlsen & Maslovat, 2019; Valls-Solé et al., 1995). The sudden auditory stimuli result in a decrease in the time it takes to initiate the planned action (Carlsen & Maslovat, 2019; Marinovic & Tresilian, 2016) and an increase in the rate of force development (RFD) (Anzak et al., 2011; Fernandez-Del-Olmo et al., 2014; Marinovic & Tresilian, 2016).

Limited research exists regarding the influence of the RST on strength gains in healthy human subjects. Notably, only one recent cross-sectional study has investigated the excitability of the RST in a comparative context, focusing on elite-level rock climbers who engage in grip strength-training and recreationally active individuals without such training. While no differences were observed in reaction times between the two groups, individuals with a history of chronic rock climbing displayed greater strength and a more pronounced RFD during startling stimuli than the recreationally active group. These findings imply that persistent grip training in rock climbing enhances the efficiency of the RST and its synaptic input to α -motoneurons (Colomer-Poveda et al., 2023). Nevertheless, the outcome concerning reaction time does not align with findings from non-human primate research, prompting the need for additional investigation (Glover & Baker, 2020). With the exception of the aforementioned study, prior research has predominantly focused on analysing the corticospinal responses between trained and untrained individuals. However, it is important to note that the findings pertaining to the training-related corticospinal responses have displayed inconsistency (Aagaard et al., 2020; Kidgell et al., 2017). Thus, determining the sites within the CNS that might explain strength gain should be examined with techniques that identify the loci of adaptation including, cortical, reticular, and spinal mechanisms. There are no studies that have systemically probed the sites within the CNS to identify the neural elements implicated by strength-training. Hence, our objective was to assess whether differences exist in the excitability of the

cortical, corticospinal, spinal, and reticulospinal pathways in healthy adults with a history of strength-training and those without such training. We hypothesized that individuals who consistently engage in strength-training would exhibit greater levels of excitability in the cortical, corticospinal, spinal and reticulospinal pathways when compared with individuals who lack a background in strength-training.

2 | MATERIALS AND METHODS

2.1 | Participants

We recruited 15 individuals with a history of chronic strength-training (≥ 2 years of experience; mean age = 24 ± 7 years, 4 females) and 11 age-matched healthy volunteers who had not engaged in any previous strength-training (mean age = 26 ± 8 , 6 females). Their lack of prior strength-training experience was confirmed through detailed questionnaires and personal interviews. Chronically strength-trained participants had a history of engaging in various upper limb exercises that directly or indirectly contributed to the improvement of wrist flexor muscles and grip strengths. These activities included holding heavy dumbbells, using grip trainers, performing deadlifts and pull-ups, and participating in boxing training, all of which played a role in enhancing wrist flexor and grip strength. These exercises were performed regularly, with an average frequency of ≥ 4 sessions per week, each lasting ≥ 60 min, over a span of more than 2 years. The majority of participants were right-handed (as determined by the Edinburgh handedness inventory), with only two exceptions (who were ambidextrous). Before participating, all individuals received comprehensive verbal explanations of the study procedures, including a thorough discussion of associated risks and benefits. Those willing to take part then provided written informed consent. Participants were carefully screened to ensure their suitability for transcranial magnetic stimulation (TMS) based on an adult safety screening questionnaire (Keel et al., 2001). It is important to note that the selected participants had no history of neurosurgery, neurological disorders such as epilepsy, orthopaedic issues or musculoskeletal upper limb injuries. Additionally, participants were not currently using any medications known to affect the nervous system and reported no hearing-related impairments. This study received ethical approval from the Monash University Human Research Ethics Committee (Project ID: 34634), and all experimental procedures were conducted in strict accordance with the principles outlined in the Declaration of Helsinki.

2.2 | Experimental setup

Participants made two visits to the laboratory; one for a familiarisation session, which included practice in performing maximum voluntary force (MVF) and the StartReact protocol, and another for the main testing session. Before the testing session, participants were instructed to avoid engaging in strenuous exercise (specifically, strength-training) for 48 h leading up to the session, as well as to abstain from consuming caffeinated and alcoholic beverages on the day of the session. During the testing session, participants were seated comfortably in a chair with the shoulders adducted, arms flexed 90° at the elbow, both forearms in the neutral and midway position between pronation and supination, and their wrists in neutral position (0° , with no extension or flexion). Bilateral grip force, quantified as the MVF, was assessed employing a hand-held grip dynamometer (Biometrics G200, Serial Number: M25789, Wilmington, DE, USA). To maintain accuracy, the inter-handle distance of the dynamometer was tailored to the anatomical characteristics of each participant's hands. This adjustment involved setting the distance at 50% of the measurement from the tip of the middle finger to the metacarpophalangeal flexion crease located at the base of the thumb.

Participants executed a warm-up protocol encompassing grip contractions, consisting of three contractions conducted at intensities of 20%, 50% and 75% of their perceived MVF. Following this, participants then conducted two MVF trials of 3–5 s-long hand grips, separated by 60 s of rest. Continuous verbal encouragement to squeeze the dynamometer as hard as possible was provided. Real-time visual feedback of force levels was delivered to the participants through a computer monitor positioned at a distance of 1 m in front of them. The maximum value recorded was considered as the MVF value (separately for each limb), and a third trial was administered if the difference between the first two trials exceeded 5%. We have reported that this method has demonstrated high reliability, with an ICC value of .981 (Walker et al., 2013).

After establishing the MVF, surface electromyography (sEMG) was conducted on the dominant arm (as determined by the Edinburgh Handedness Inventory; Oldfield, 1971). Surface electrodes were affixed to the skin using adhesive tape and positioned over the muscle belly of the flexor carpi radialis (FCR) in the proximal third of the forearm (Gueugneau et al., 2017). Subsequently, for both the strength and non-strength trained groups, measures of strength/MVF, cortical excitability, corticospinal excitability, spinal excitability (cervicomedullary motor-evoked potentials [CMEPs]), cortico-reticulospinal response (iMEPs) and RST excitability

were examined. For the normalization of corticospinal responses, peripheral maximal compound wave (M_{MAX}) was assessed by using peripheral electrical stimulation at 10% MVF (for the dominant limb) (Figure 1).

2.3 | sEMG and TMS measurements

sEMG recording was performed using bipolar Ag–AgCl electrodes, 10 mm diameter, placed consecutively with an interelectrode distance of 2 cm over the FCR muscle belly at one third of the distance from the medial epicondyle to the radial styloid (Gueugneau et al., 2017) in line with the muscle fibres orientation. The electrode placement area was cleaned with 70% isopropyl alcohol. sEMG activity was then recorded from both the left and right FCR muscles. To ensure a common reference point, a grounding strap was placed around the wrist of the opposite limb.

The TMS comprised of two Magstim 200² stimulators (Magstim Co, Dyfed, UK), connected through a

Bistim unit, and a single figure-of-eight coil with an external diameter of 70 mm per loop. We determined the motor hotspot exclusively for the dominant FCR muscle, inducing current flow in the cortex from posterior to anterior with the TMS coil position 45° relative to the sagittal plane. Active motor thresholds (AMTs) were established by identifying the stimulation intensity at which at least five out of 10 stimuli generated motor-evoked potentials (MEPs) amplitudes exceeding 200 μ V for AMT in the FCR muscle during 10% MVF (Cohen et al., 1998).

Recruitment curves were constructed by measuring the amplitude of MEPs elicited through single-pulse TMS at various stimulus intensities, specifically at 130%, 150% and 170% of AMT to assess corticospinal excitability. The method we employed to gather and construct our recruitment curves has previously demonstrated extremely high reliability, as indicated by an ICC of .96 (Carson et al., 2013). To evaluate corticospinal inhibition, we examined the cortical silent period at these differing intensity levels. Paired-pulse TMS was used to investigate

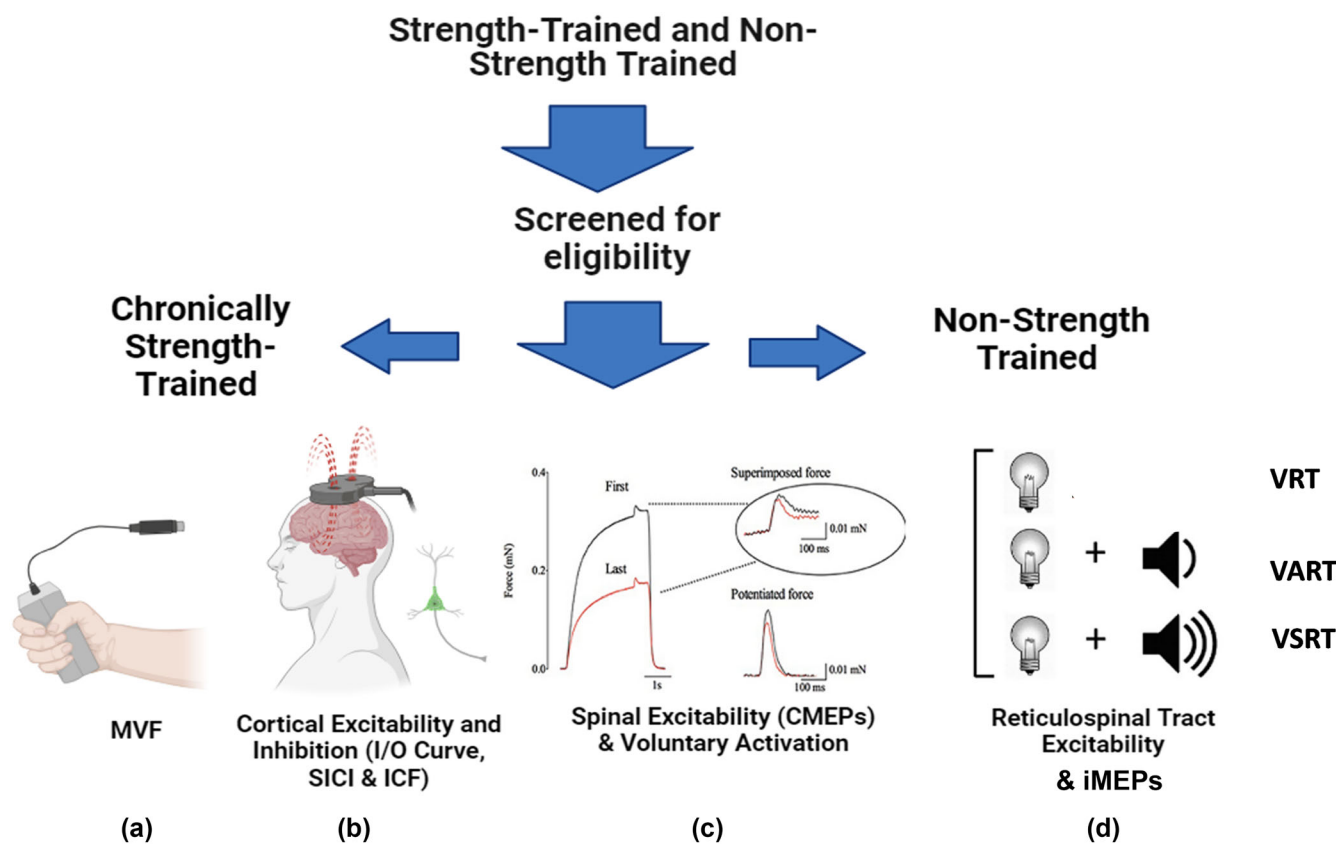


FIGURE 1 Experimental setup. (a) Participants performed grip contraction. (b) Cortical and corticospinal excitability examined using transcranial magnetic stimulation (TMS). (c) Spinal level excitability (cervicomedullary motor-evoked potential [CMEP]) and voluntary activation examined by transmastoid and peripheral nerve stimulation. (d) Reticulospinal excitability examined by StartReact protocol and ipsilateral motor-evoked potential (iMEP). ICF, intracortical facilitation; I/O, input output curve; MVF, maximum voluntary force; SICI, short-interval cortical inhibition; VART, visual acoustic reaction time; VRT, visual reaction time; VSRT, visual startling reaction time.

excitability at the cortical level, including intracortical facilitation (ICF) and SICI. We have previously demonstrated good to excellent reliability for paired-pulse TMS, with ICC values ranging from .62 to .80 (Presland et al., 2023). SICI was induced by delivering a conditioning stimuli (CS) at a subthreshold level (80% AMT) and subsequent test stimuli (TS) at a suprathreshold level (130% AMT), with an interstimulus interval of 3 ms. ICF was elicited by applying the same stimuli at 10 ms intervals. To mitigate the effects of fatigue, we incorporated a 1-min rest period between these tests.

We also assessed iMEPs at an intensity level corresponding to 100% of the maximum TMS output, with participants maintaining a robust bilateral contraction of the FCR muscle at 50% of their MVF. The TMS coil was accurately positioned anteromedially to the hotspot associated with the contralateral MEP (cMEP) (Maitland & Baker, 2021).

2.4 | Maximal compound muscle action potential and voluntary activation

We evaluated the maximal compound muscle action potential (M_{MAX}) to serve as a normalization reference for TMS responses. Electrical stimulation was administered to the brachial plexus using a pulse width of 200 μ s delivered by a DS8R Bipolar constant current stimulator from Digitimer, UK. The cathode, which had a diameter of 10 mm and was made of Ag–AgCl, was positioned at Erb's point, while the anode was placed over the acromial process of the shoulder. This stimulation aimed to measure the direct muscle response of the FCR muscle, which occurred during background muscle activity involving isovolumetric contraction at 10% MVF. To obtain M_{MAX} , we initiated stimulation at Erb's point with low intensity and progressively increased it until no further increase in the M_{MAX} was observed. This was further confirmed by increasing the current by an additional 20% to achieve a similar M-wave amplitude, indicating that M_{MAX} had been reached. This measurement represented the peak-to-peak amplitude of the sEMG response. We have previously demonstrated good to good reliability for M_{MAX} , with an ICC of .92 (Walker et al., 2013).

Voluntary activation (VA) was also assessed by applying a single high-voltage electrical stimulation (pulse width: 200 μ s) to Erb's point during the maximum contraction state to induce a superimposed twitch and, during rest, to elicit a resting twitch in the dominant FCR muscle. To accommodate the potential scenario where electrical stimulation may not have been administered

precisely at the moment of peak force production (maximum torque [T_{MAX}]), we employed the formula presented by Strojnik & Komi JAP 84, 1998 (Strojnik & Komi, 1985) for the calculation of percentage of VA.

$$VA (\%) = 100 - D^* (T_B/T_{MAX})/T_{TW}^* 100$$

In this equation, 'D' represents the difference and is calculated as the contrast between the torque level immediately before the application of electrical stimulation (T_B) and the maximum torque observed after stimulation. Twitch torque (T_{TW}) denotes the maximum twitch torque or resting twitch arising from electrical stimulation applied to the relaxed FCR muscle. Again, we have previously demonstrated good to good reliability for VA, with an ICC of .73 and maximum twitch torque data of .99 (Walker et al., 2013).

2.5 | StartReact protocol

The efficiency of RST was assessed using the StartReact protocol and recording iMEPs during forceful bilateral gripping. In accordance with previous studies (Baker & Perez, 2017; Fisher et al., 2013) that utilized the StartReact protocol, we examined the StartReact response by instructing participants to react to the illumination of a light-emitting diode (LED) by executing a power grip (squeezing the dynamometer handle) as forcefully and as fast as possible, while maintaining their forearms in a neutral position. To facilitate rapid and forceful contractions, participants performed five gripping contractions for practice. Additionally, participants were exposed to loud stimuli for familiarization. They were instructed to maintain a constant baseline resting force and avoid any pre-tension or preparatory movements before the "go" signal. The LED, serving as a visual cue, was positioned one metre in front of the participants and was accompanied by one of three auditory stimuli presented in a randomized order: (1) a loud/startle sound (115–120 dB; 500 Hz, 50 ms); (2) a quiet sound (80 dB; 500 Hz, 50 ms); or (3) no sound. A total of 60 trials were conducted with a 5–13 s interval, comprising 20 trials for each stimulus type, presented randomly. Prior to commencing the main study, we conducted pilot testing among eight healthy young adults to assess the reliability of the StartReact paradigm in the FCR. The results revealed intraclass correlation coefficient (ICC) values of .5 for visual reaction, .60 for visual acoustic reaction time and .86 for visual startle reaction time, respectively. These findings align with those reported by Colomer-Poveda et al. (2023).

2.6 | Cervicomedullary motor-evoked potential (CMEP)

We assessed the excitability of the corticospinal tract at the spinal level through high-voltage electrical stimulation using transmastoid electrodes (200 μ s duration, DS8R Bipolar constant current stimulator, Digitimer, UK) placed on the skin overlying each mastoid process (Taylor & Gandevia, 2004). This stimulation was carried out while the FCR muscle was actively contracting at 50% MVF, and the measurement obtained for CMEP was assessed as the peak-to-peak amplitude of the non-rectified EMG response. Latency, between the artefact and the response, was also investigated, and the onset of CMEP was determined at the point where the rectified sEMG reached a value twice the standard deviation (SD) calculated across a 200 ms interval of the pre-stimulus activity. This method has been shown to be reliable with an ICC of .816 (Yacyshyn et al., 2020).

2.7 | Data analysis

The sEMG activity of the FCR muscle before each TMS stimulus was assessed 100 ms prior to the stimulation. Trials were discarded if the pre-stimulus *rmsEMG* exceeded $5 \pm 1\%$ of the maximum *rmsEMG*, and these trials were repeated. The peak-to-peak amplitude of MEPs was measured in the dominant FCR muscle. MEPs were analysed using LabChart 8 software by ADInstruments after each stimulus was automatically flagged with a cursor, providing peak-to-peak values in mV. These values were then averaged, normalized to the M_{MAX} and multiplied by 100.

To calculate the total area under the recruitment curve (AURC), the trapezoidal integration method was employed, utilizing the actual data collected during the construction of corticospinal excitability (MEP amplitude) and corticospinal inhibition (silent period duration) recruitment curves for the FCR. The experimenter remained blinded to each condition throughout the AURC analyses.

Silent period durations were obtained from single-pulse stimuli delivered within the construction of the recruitment curve at 130%–170% of AMT. These durations were determined by observing the time between the onset of the MEP and the resolution of background sEMG, which was visually inspected and marked manually. The average duration 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.

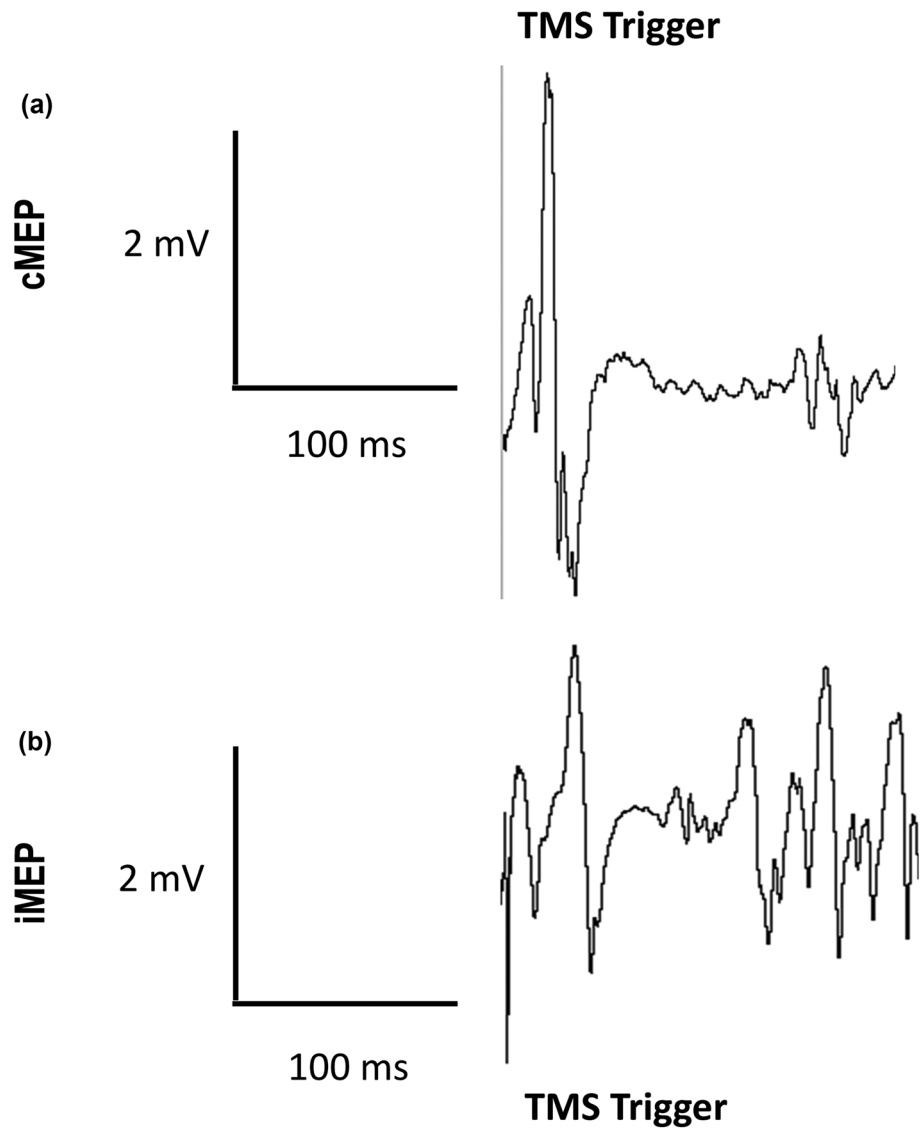
TMS applied to the M1 can lead to the activation of reticulospinal cells through corticoreticular connections (Fisher et al., 2012). Thus, we measured both cMEPs and iMEPs during bilateral contractions of the wrist flexors. Following the determination of the latency difference between the onset of cMEP and iMEP, we excluded data from subjects where this difference was less than 5 ms (Maitland & Baker, 2021). This exclusion was based on the possibility that such short latency differences might result from direct activation of the contralateral cerebral hemisphere due to current spread (Ziemann et al., 1999), rather than reflecting a genuine iMEP response. We determined the ipsilateral-to-contralateral amplitude ratio (ICAR) following the methodology outlined in the work of Bawa et al. (2004). Larger ICAR values signify a higher degree of muscle control by the reticulospinal system, while smaller ICAR values suggest a greater influence of the corticospinal system on muscle control (Figure 2).

We assessed participants' reaction times in response to visual stimuli (visual reaction time [VRT]), visual stimuli combined with a quiet sound (visual auditory reaction time [VART]) and visual startling stimuli (visual startling reaction time [VSRT]). Reaction times were determined by measuring the onset latency of sEMG activity in the FCR muscle following each stimulus or cue. sEMG onset was defined as the point at which the sEMG value exceeded the mean rectified sEMG value measured 200 ms before the stimulus by ± 3 SD (Baker & Perez, 2017). Data analysis was performed using a custom-written macro in LabChart (ADInstruments, Bella Vista, Australia), and each trial was manually checked for potential errors in sEMG onset detection by the macro, which may arise from electric noise artefacts or pre-stimulus activity. Manual adjustments to onset detection were made when inappropriate detections were visually identified by the software. Trials with a mean rectified sEMG value that deviated beyond ± 2 SD from the mean rectified sEMG value measured 100 ms before any of the stimuli were considered as indications that the participants were not at rest and were therefore excluded. Reaction times exceeding 700 ms were also excluded (Sangari & Perez, 2020). Among the three stimuli types, the startling stimulus was demonstrated to activate the reticular formation or the RST, resulting in shortened reaction times. To normalize the data, we estimated the reticulospinal gain as the ratio of the change in reaction time following startling stimuli to the change in reaction time following the quiet sound:

$$\text{StartReact gain} = \frac{[VRT - VSRT]}{[VRT - VART]}$$

(Baker & Perez, 2017).

FIGURE 2 (a) Contralateral motor-evoked potential (cMEP) and (b) ipsilateral MEP (iMEP) latencies and amplitude from one participant. TMS, transcranial magnetic stimulation.



Furthermore, we evaluated the RFD during the first 50 ms and the subsequent 50–100 ms following the initiation of force in the three conditions. This approach was based on a prior study (Colomer-Poveda et al., 2023) that investigated the effect of startling stimuli on RFD during these specific intervals. The onset of force (time 0 ms) was determined as the moment when the force signal value exceeded 3 SD from the value recorded 200 ms prior to the stimulus (Anzak et al., 2011; Colomer-Poveda et al., 2023).

2.8 | Statistical analysis

The sample size for this study was determined using G*Power software (version 3.1.7.9). To calculate the sample size for each group, we utilized a pooled effect size of 1.12 for a decrease in SICI following strength-training.

This effect size was derived from a systematic review and meta-analysis conducted by Siddique et al. (2020), which aimed to identify potential sites of neural adaptation following strength-training.

The statistical power (β) was set to .80, and the significance level (α error probability) was set at .05. Accordingly, the final determined sample size for the study was 28 participants (14 in each group). However, three untrained participants were unable to complete the measurements due to discomfort with electrical stimulation at the brachial plexus, a central step for determining the M_{MAX} necessary for normalizing MEPs.

To address concerns about potential withdrawals due to discomfort, an additional participant was included in the trained group as a precautionary measure. It is noteworthy that all trained participants (15 in total, including the precautionary addition) successfully completed all measurements.

Demographic, anthropometric, MEPs (TMS) and StartReact data were analysed in SPSS (version 26). Shapiro-Wilk's test was used to assess the normality of distribution and homogeneity of variances was assessed by Mauchly's test of sphericity and Levene's test of equality. For the StartReact data, VART data was not normally distributed and instead was log-transformed.

Descriptive quantitative values including age, MVF, stature, mass and M_{MAX} were presented as mean \pm SD in the text. Independent *t*-tests were used to examine any significant difference in gripping strength, AMT, M_{MAX} , SIC1, ICF, cortical silent period (CSP), StartReact gain, VA and CMEP between trained and untrained groups. For iMEP, due to violations of normality, a Mann-Whitney U test was conducted on the median ICAR ratios. Repeated measures of three-way ANOVA was employed to determine the effect of strength-training status (chronically trained versus untrained), and different StartReact conditions (VRT, VART, VSRT) on the RFD in the first 50 ms, and 50–100 ms following the onset of force. StartReact conditions and time intervals were taken as repeated measure factors (within-subject factors), while strength-training status was taken as a between-subjects factor. Repeated measures of two-way ANOVA was also employed to examine the effect of strength-training status (chronically trained vs. untrained) and different StartReact conditions (VRT, VART, VSRT) on reaction time. StartReact conditions were considered as repeated measure factors. Post hoc pairwise comparisons, including Bonferroni analysis, were conducted to examine individual dependent measures. Additionally, effect size in the form of partial eta square (η^2) was utilized to assess the magnitude of comparative effects. We utilized partial eta square (η^2) when addressing multiple independent variables in the context of two-way or three-way ANOVA. In addition, we employed eta square as a measure of effect size in independent *t*-test analyses, as recommended by GraphPad Prism. Partial eta squared specifically focuses on the unique contribution of a particular independent variable while considering the influence of other variables. It effectively accounts for and isolates the impact of other independent variables and interactions, thereby removing their influence from the analysis. In essence, partial eta squared provides valuable insight into the magnitude of the effect exerted by the independent variable on the dependent variable (Cohen, 1973; Richardson, 2011). Effect sizes of .01, .06 and .14 were employed to classify effects as small, moderate and large (Cohen, 1973), in cases where significant multivariate effects were detected. The level of significance used for all tests was set at $p < .05$. All data are presented as mean \pm SD.

3 | RESULTS

In this study, a total of 26 participants took part, consisting of 15 individuals with a chronic history of strength-training (averaging 6.4 ± 7.0 years of strength-training experience) and 11 untrained volunteers. The mean height of the trained participants was 173.5 ± 10.1 cm, while the untrained participants had an average height of 167.5 ± 9.5 cm ($p = .14$). Regarding weight, the mean weight for the trained participants was 77.3 ± 13.2 kg, and for the untrained participants, it was 67.3 ± 17.3 kg, with no significant difference observed ($p = .10$, Table S1).

3.1 | MVF and corticospinal excitability

The maximum voluntary force, assessed via hand grip strength, displayed a significant difference between individuals who had undergone chronic strength-training (59% difference) and those who were not trained ($p < .001$; $\eta^2 = .43$). To mitigate the confounding effect of muscle mass, MVF was normalized to body weight. The body weight normalized MVF was also higher in the chronically trained group than the non-trained group ($p = .003$; $\eta^2 = .31$) (Figure 3). When examining the AURC representing the intensity of TMS at 130%, 150% and 170% of AMT on the X-axis against the normalized

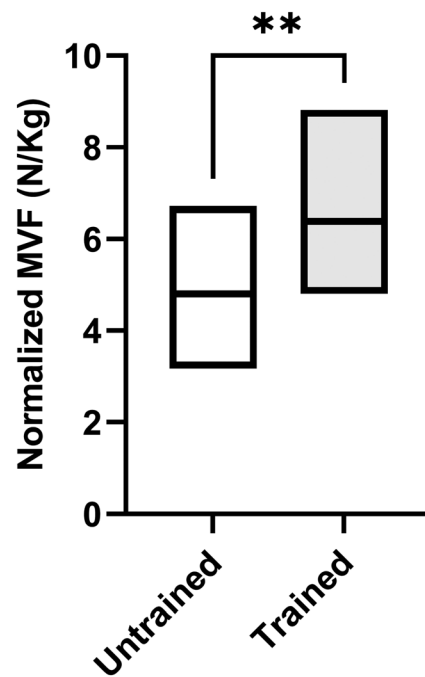


FIGURE 3 Maximum voluntary force (MVF) normalized to body weight in trained and untrained participants. * denotes difference between trained and untrained participants, $p < .05$.

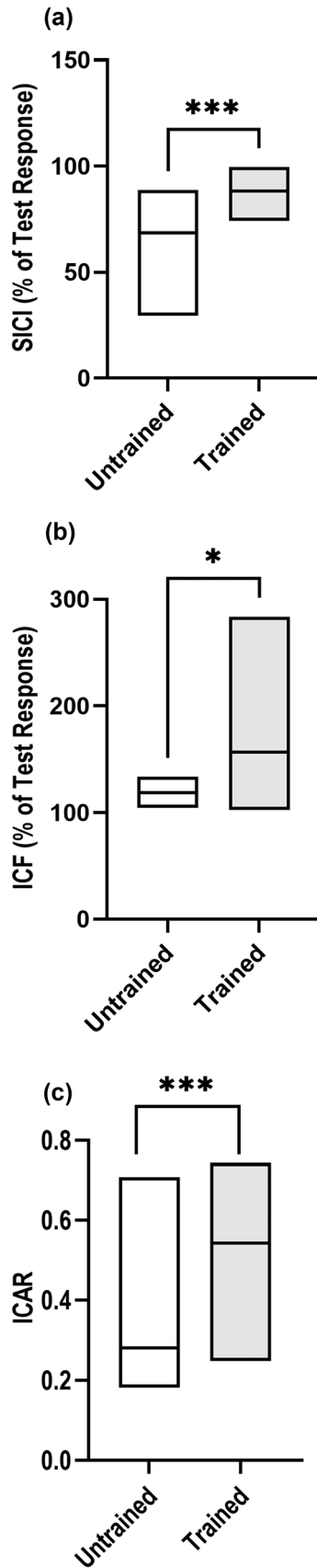


FIGURE 4 (a–c) Mean \pm standard deviation (SD) for short-interval cortical inhibition (SICI) (4a), intracortical facilitation (ICF) (4b) (expressed as a percent of the test response) and ipsilateral-to-contralateral amplitude ratio (ICAR) (4c) in trained and untrained participants. * denotes difference between trained and untrained participants, $p < .05$.

MEP amplitude relative to M_{MAX} on the Y-axis, no significant difference was observed between the strength-trained and untrained adults ($t(24) = 2.01$, $p = .05$). Furthermore, the comparison of the AURC for cortical silent period durations revealed no significant difference between the strength-trained and untrained participants ($t(24) = .402$, $p = .69$; Table S1).

3.2 | Cortical inhibition and facilitation

The trained group showed a reduction in SICI, with a mean value of $88 \pm 8.0\%$, compared with the untrained group, which showed a higher SICI level with a mean of $69 \pm 17.5\%$ ($t(23) = 3.8$, $p < .001$, $\eta^2 = .38$, Figure 4). Furthermore, the chronically trained participants displayed a higher level of ICF, $156 \pm 49\%$, compared with the untrained participants (Figure 4b), who had a mean of $118 \pm 9\%$ ($t(23) = 2.5$, $p = .02$, $\eta^2 = .21$).

3.3 | Ipsilateral motor-evoked potentials (iMEPs) and ICAR

An additional aim was to explore the potential role of the reticulospinal system in the context of strength-trained participants compared with nontrained. ICAR values varied widely between individuals (range .182–.743). Mann–Whitney U test was performed to compare ICAR ratios between strength-trained ($n = 11$, four females) and nontrained ($n = 8$, four females). It was only possible to elicit iMEPs in 11 out of 15 participants (73%) of the strength-trained group and 8 out of 11 participants (73%) in the untrained group. There was a larger ICAR response in the trained (Figure 4c) compared with the untrained group ($p = .03$). Additionally, the effect size measure of .92 suggested a large effect size, signifying a meaningful difference in ICAR ratios between strength-trained and untrained.

3.4 | StartReact responses

A repeated measures ANOVA revealed no significant effect of group (training status) ($F_{1,22} = .739$, $p = .39$) but

did indicate an effect of condition (VRT, VART and VSRT) ($F_{2,44} = 469$, $p < .001$, $\eta^2 = .96$), as well as a significant interaction between group and condition ($F_{2,44} = 6.2$, $p = .004$, $\eta^2 = .22$) on reaction time. Notably, only the VSRT significantly shortened reaction time in the strength-trained participants (47 ± 16 ms) compared with untrained participants (71 ± 26 ms, $p = .01$). There were no significant differences in reaction time between groups following VART ($t(22) = 1.3$, $p = .20$) and VRT ($t(22) = .76$, $p = .45$) conditions. Considering the condition as a within-subject factor, it had a significant effect on reaction time. Pairwise comparisons revealed that VSRT (57 ± 24 ms) was significantly shorter compared with VRT (150 ± 26 ms, $p < .001$) and VART (95 ± 26 ms, $p < .001$; Table S2).

To confirm these changes in reaction time were related to changes in RST excitability, the reticulospinal gain was calculated and compared between strength-trained and untrained. The results showed that reticulospinal gain in the strength-trained participants (2.5 ± 1.4) was significantly higher compared with the untrained group (1.3 ± 0.3) ($t(22) = 2.5$, $p = .02$) (Figure 5).

Regarding RFD, a three-way repeated measures ANOVA demonstrated that the RFD in the strength-trained group (3362 ± 859 N·s⁻¹) was significantly higher than that of the untrained group (1754 ± 615 N·s⁻¹) ($F_{1,22} = 21$, $p < .001$, $\eta^2 = .49$). Nearly half (49%) of the variation in the RFD was attributed to strength-training status. To account for the effect of muscle size, RFD was

also normalized to body mass. The normalized RFD was higher in the trained group (38.8 ± 10.1 N·s⁻¹/kg) compared with the non-trained group (26.3 ± 10.12 N·s⁻¹/kg) ($F_{1,22} = 8.8$, $p = .007$, $\eta^2 = .29$). Twenty-nine percent of the variation in normalized RFD was attributed to strength status. Time interval ($F_{1,22} = 69.7$, $p < .001$, $\eta^2 = .76$), condition ($F_{2,44} = 7.00$, $p = .002$, $\eta^2 = .24$), and the interaction of condition and group (strength-training status) ($F_{2,44} = 6.3$, $p = .004$, $\eta^2 = .22$) had a significant effect on RFD. Pairwise comparisons revealed that normalized RFD during startling auditory stimulus (S) (34.8 ± 10.8 N·s⁻¹/kg) was higher compared with the normalized RFD during non-startling auditory stimulus (A) (31.6 ± 11.7 N·s⁻¹/kg, $p = .003$) and visual stimulus only (V) (31.4 ± 8.8 N·s⁻¹/kg, $p = .007$). Additionally, normalized RFD during the time interval of 50–100 ms (38.3 ± 10.8 N·s⁻¹/kg) was higher compared with the first 50 ms (26.9 ± 11.0 N·s⁻¹/kg, $p < .001$). In the trained group, a higher normalized RFD (28 ± 8.2 N·s⁻¹/kg) was observed during S compared with A (25.6 ± 7.01 N·s⁻¹/kg) ($t(13) = 4.8$, $p < .001$) and V only (25.9 ± 6.4 N·s⁻¹/kg) ($t(13) = 3.1$, $p = .009$), but not for the non-trained group (S vs. A: $t(9) = .03$, $p = .97$; S vs. V: $t(9) = .11$, $p = .91$; A vs. V: $t(9) = .14$, $p = .89$). (Figure 6).

3.5 | Cervicomedullary motor evoked potentials

Transmastoid electrical stimulation was successfully elicited to produce CMEPs in only four untrained (only 36%) and nine strength-trained participants (60%). There

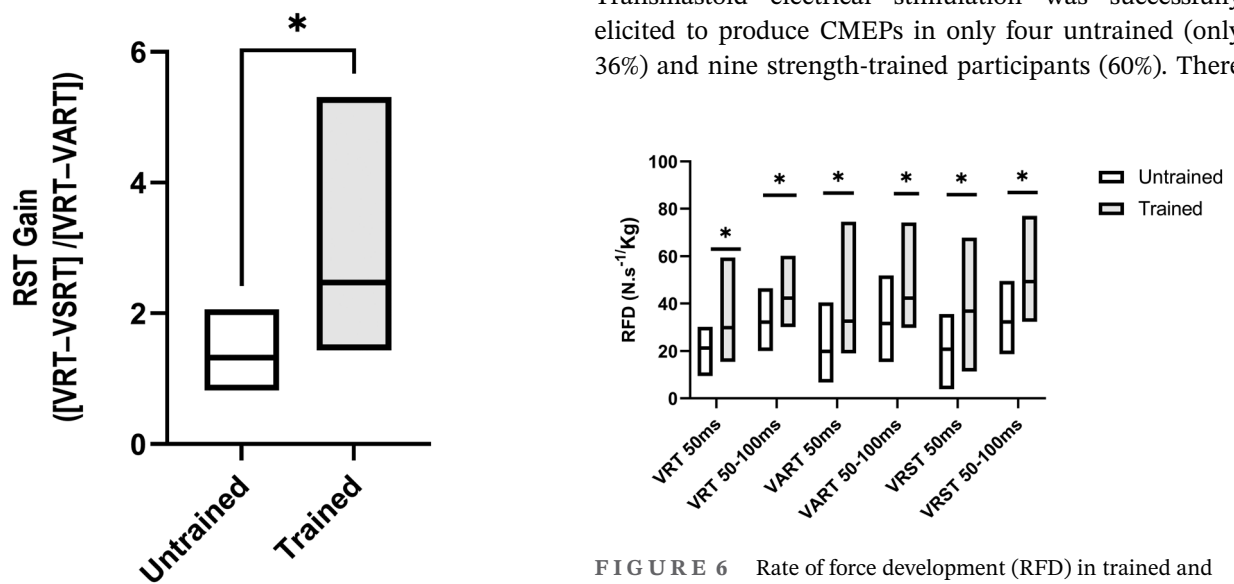


FIGURE 6 Rate of force development (RFD) in trained and untrained participants in the interval of first 50 ms and 50–100 ms following a visual cue accompanied by either of visual acoustic reaction time (VART), visual startling reaction time (VSRT) or visual reaction time (VRT). * denotes difference between trained and untrained participants, $p < .05$. ms, milliseconds; N·s⁻¹/kg, Newton per second.

FIGURE 5 Reticulospinal gain in trained and untrained adult participants. * denotes difference between trained and untrained participants, $p < .05$. FCR, flexor carpi radialis; VART, visual acoustic reaction time; VRT, visual reaction time; VSRT, visual startling reaction time.

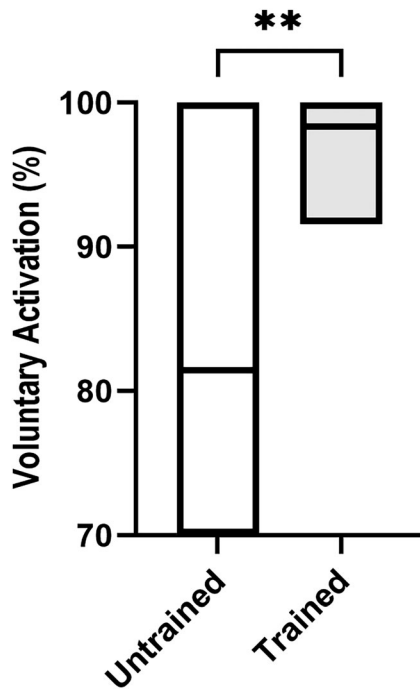


FIGURE 7 Voluntary activation in trained versus untrained adult participants. * denotes difference between trained and untrained, $p < .05$.

was no difference observed in the CMEP amplitude (expressed as a percent of M_{MAX}) between the strength-trained group (29.5 ± 14.8) and the untrained group (53.5 ± 32.5 ; $t(11) = 1.84$, $p = .09$).

3.6 | Voluntary activation

VA assessments were conducted on nine of the untrained participants (82%, two participants chose not to undergo VA assessment because they found the stimulation uncomfortable) and 13 of the strength-trained participants (87%, for the same reasons as the two untrained participants). The results revealed that the strength-trained group had a higher VA ratio ($98 \pm 3.2\%$) compared with the untrained group ($81 \pm 17\%$) ($t(20) = 3.5$, $p = .002$, $\eta^2 = .38$) (Figure 7).

4 | DISCUSSION

This comparative cross-sectional study examined possible sites of adaptations to strength-training by comparing the cortical, corticospinal, and reticulospinal responses in chronically strength-trained versus untrained participants. We assessed cortical and corticospinal excitability through the application of TMS and evaluated reticulospinal efficacy by comparing the effect of a startling

stimulus on reaction time and RFD during forceful gripping with the dominant hand in chronically strength-trained versus untrained individuals. In addition, we measured iMEPs during bilateral gripping to assess corticoreticular activation. Greater excitability of M1 (a higher motor cortical excitability) and the RST was found in chronically strength-trained participants as compared with the untrained participants. There were no differences in corticospinal and/or spinal excitability between the two groups.

A greater level of cortical facilitation (ICF) and reduced cortical inhibition (SICI) was observed in the chronically strength-trained group. This finding is consistent with prior research where a reduction in SICI was evident following heavy-load strength-training (Weier et al., 2012). Lower SICI (i.e. reduced inhibition) has been observed in the context of strength-training with skilled techniques (Pascual-Leone et al., 1995; Smyth et al., 2010). Additionally, there have been reports indicating that strength-training induces modifications in the cortical inhibitory networks (Škarabot et al., 2020). Data from the current investigation suggested that chronic strength-training led to a reduction in the threshold required for the activation of intracortical facilitatory circuits (Lahouti et al., 2019). Considering that cortical outputs depend on the balance between inhibitory and facilitatory circuits (Peurala et al., 2008), the strength-trained group, exhibiting higher ICF and lower SICI, which typically mitigate the standard inhibition of cortical projections to muscles (Zoghi & Nordstrom, 2006), may have led to increased cortical excitability. At a minimum, strength-training seems to increase the corticomotor drive to the contracting muscles in the strength-trained group. This line of inquiry is supported by the increase in VA within the chronic strength-training group. Accordingly, long-term strength-training leads to substantial network modulation, involving the coordinated targeting of both GABAergic (GABA_A) and glutamatergic neurons. This coordinated action serves to reduce synaptic inhibition while concurrently enhancing synaptic facilitation. This, in turn, yields increased activation of α -motoneurons, which is likely a pivotal factor contributing to the differences observed in MVF (when normalized to body mass).

The higher level of VA observed in individuals engaged in chronic strength-training also suggests that strength-trained participants have the ability to recruit and/or discharge their α -motoneurons to a greater extent, enabling them to generate greater maximum force (Herbert & Gandevia, 1999), which is unsurprising given strength-training is commonly hypothesized to increase neural drive to the trained musculature (Aagaard et al., 2002; Tøien et al., 2018). Thus, the higher MVF or strength exhibited by the chronically strength-trained

group likely stems from the improved neural drive (among other factors) directed toward the trained muscles, conceivably rooted in cortical adaptations subsequent to prolonged strength-training. Moreover, the noted elevation in MVF among participants engaged in strength-training could be linked to muscle hypertrophy induced by prolonged training. It is expected that individuals involved in such training regimens would undergo hypertrophy in their muscles.

While a difference in intracortical excitability was evident between the two groups, it is worth noting that no significant difference in corticospinal excitability was observed, which is consistent with findings reported in other studies (del Olmo et al., 2006; Tallent et al., 2013). However, the RST was also examined using the StartReact protocol and calculating the ICAR ratio, based on which, the reticulospinal gain was found to be significantly higher in the chronically strength-trained group than in the untrained group. The interaction of condition or type of cue and strength status was found to be associated with reaction time. The striking finding here is that the startling stimuli led to a notable reduction in reaction time exclusively within the chronically strength-trained group. This new empirical evidence supports the idea that strength-training enhances efficacy in the rapid response task due to adaptations that are induced by chronic strength-training through the pontomedullary reticular formation. These adaptations likely manifest as an increased firing rate of α -motoneurons, ultimately culminating in the observed reduction in reaction time following the startling cue (Škarabot et al., 2022).

Furthermore, the execution of the pre-planned gripping action exhibited notably reduced latency when prompted by the startling cue as compared with both the visual and visual-auditory cues. These findings align with previous research, which has consistently demonstrated that startling cues have the capacity to reduce response latency (Carlsen et al., 2004a; Colomer-Poveda et al., 2023; Škarabot et al., 2022). The rapid execution of a pre-planned task, such as gripping, in response to the presentation of an imperative visual cue accompanied by a sudden, loud startling stimulus is thought to be a consequence of the startling stimulus activating and eliciting the involuntary release of the pre-planned motor programme stored within subcortical circuits (Carlsen et al., 2004b; Carlsen et al., 2003; Valls-Solé et al., 1999), likely within the pontomedullary formation (Carlsen et al., 2004b; Carlsen & Maslovat, 2019). This process bypasses cortical pathways, leading to the enhanced recruitment of α -motoneurons (Carlsen & Maslovat, 2019).

The introduction of startling stimuli also exerted a notable influence on RFD during pre-planned forceful contractions. In response to the startling cues, RFD

exhibited a marked increase when compared with responses evoked by visual, acoustic, and visual-acoustic stimuli in both participant groups, aligning with prior investigations demonstrating the augmenting effect of startling stimuli on RFD (Anzak et al., 2011; Colomer-Poveda et al., 2023; Fernandez-Del-Olmo et al., 2014; Škarabot et al., 2022). This increase in RFD is likely attributed, in part, to improved recruitment of motor units (Del Vecchio et al., 2019; Dideriksen et al., 2020), a phenomenon possibly induced by the activation of the pontomedullary reticular formation by startling stimuli (Carlsen et al., 2004b; Koch et al., 1992). Another conceivable factor contributing to the greater RFD following startling cues is the synchronization of motor unit discharge rates, an effect that has been documented in the literature (Škarabot et al., 2022). Therefore, the greater RFD observed following startling stimuli is likely a result of faster recruitment, increased discharge rates, and enhanced synchronization of motor units (Del Vecchio et al., 2019; Dideriksen et al., 2020; Van Cutsem et al., 1998), influenced at least in part by subcortical structures (i.e. the pontomedullary reticular formation) (Škarabot et al., 2022).

The strength of an individual was identified as another pivotal factor influencing RFD. In agreement with previous research (Colomer-Poveda et al., 2023), our findings demonstrated a significant increase in RFD within the strength-trained group compared with the untrained group. Furthermore, research involving non-human primates, employing direct and invasive techniques to probe alterations in the RST, have explained how chronic strength-training induces neural adaptations within RST circuits, culminating in enhanced RST efficiency (Glover & Baker, 2020). Consequently, it is reasonable to suggest, that prolonged strength-training in humans fosters greater excitability within the RST, consequently strengthening synaptic input from the RST to α -motoneurons (Atkinson et al., 2022; Glover & Baker, 2020). Also, prior research has clarified that strength-training has the ability to accelerate the activation of larger motor units (Del Vecchio et al., 2018). Consistent with the findings of Colomer-Poveda et al. (2023), it was observed that the RFD during the 50–100 ms interval exceeded that of the initial 50 ms interval. The higher RFD observed during the 50–100 ms interval compared with the 0–50 ms interval is likely attributable to several factors, but, namely, the recruitment of larger motor units with fast-twitch muscle fibres, increased firing rates, more efficient cross-bridge cycling and enhanced neuromuscular coordination (Del Vecchio, 2023).

Of particular interest, the group engaged in chronic strength-training, which demonstrated a significant increase in strength and greater RFD, displayed larger

ICAR values. This observation lends support to the proposition that strength-training enhances the functionality of the RST, as supported in previous work (Glover & Baker, 2020). This outcome illustrates that individuals with greater strength indeed exhibit larger ICAR values, which serve as an indicator of more prominent RST projections. Furthermore, our observations regarding greater RFD align with findings from several prior investigations (Carlsen et al., 2004b; Davis et al., 1982; Koch et al., 1992). The increase in RFD and shortened reaction times following startling stimuli are likely rooted in the activation of neurons within the subcortical structures (namely, the pontomedullary reticular formation). We observed that reaction time was significantly shorter in the trained group compared with the untrained group, but only following the presentation of startling stimuli (VSRT). This suggests that the trained group benefits from a more efficient RST (i.e. greater excitability) mediated by chronic strength-training.

Although we did not observe any differences in corticospinal excitability and inhibition between the strength-trained and untrained groups, it is important to acknowledge that the influence of cortical factors on RFD cannot be entirely discounted (Marinovic & Tresilian, 2016). The M1 plays a contributing role in the observed increase in RFD. Supporting this view, our study revealed that the strength-trained group, characterized by higher RFD, exhibited lower cortical inhibition and greater cortical facilitation in comparison to the untrained group. Subsequently, this greater cortical excitability in the strength-trained group could have contributed to the overall improvement in RFD. For example, previous evidence showed a prominent role for the M1, especially in the early preparatory phase of rapid contractions (Baudry & Duchateau, 2021). Following the presentation of startling stimuli, the cortical inputs, potentially amplified by the extensive cortico-reticular connections, are likely further potentiated by the reticulospinal neurons, resulting in increased motor output (Škarabot et al., 2022). Indeed, our findings for RST gain, ICAR and greater cortical excitability, support a prominent role of the cortico-reticular tract in mediating strength gain.

As our study follows a cross-sectional design, it is of paramount importance to exercise caution when interpreting the findings and when seeking to establish a definitive cause-and-effect relationship between strength-training and neural adaptations, particularly those related to the RST. It is important to recognize the inherent limitations associated with cross-sectional investigations, including the inability to infer causation, the potential impact of confounding variables (even though we made efforts to control for age and biological sex

matching), and the potential for selection bias. Consequently, it becomes imperative to embark on longitudinal studies to probe deeper into and either validate or scrutinize the influence of strength-training on RST changes. An additional constraint in this study was related to specific electrophysiological measurements. The procedure for eliciting CMEPs through transmastoid electrical stimulation presented challenges for participants, making its execution difficult. Consequently, a restricted number of participants were able to undergo this procedure due to associated discomfort. The resulting small sample size may have contributed to the observed absence of between-group differences. Another limitation of the study is the absence of a measure for muscle hypertrophy. The disparity in MVF between the strength-trained and untrained groups could potentially be attributed to differences in muscle mass. Nevertheless, to address this issue, we normalized MVF to body mass, mitigating the impact of variations in muscle mass on strength gain.

5 | CONCLUSION

In the present study, chronically strength-trained individuals exhibited notable differences in several key corticoreticular and neuromuscular variables compared with individuals with no strength-training experience. These distinctions included higher levels of VA, MVF, greater ICF, lower intracortical inhibition and greater corticoreticular activation. Additionally, startling stimuli elicited a reduction in reaction time exclusively within the strength-trained group. RFD was significantly greater in the strength-trained group in comparison to the untrained group. Collectively, these findings suggest that chronic strength-training induced neural adaptations within the RST. Concurrently, alterations in intracortical circuits within the M1 elevate cortical excitability. These network modifications contribute to increased synaptic input to α -motoneurons and likely underlie the observed higher VA and MVF within the trained group.

5.1 | Future consideration and implication of the present findings

The present study provides valuable insights into the potential engagement of cortical and subcortical neural mechanisms in the process of strength development. These findings have relevance for neurorehabilitation initiatives focussed on promoting strength recovery among individuals with motor impairments. It also holds significance within the context of the ageing population, where

strength decline and alterations in reticulospinal function are common phenomena. Furthermore, these findings carry implications for strategies aimed at optimizing athletic performance through targeted interventions at these neural sites. We underscore the necessity for future longitudinal investigations to comprehensively explore the effects of strength-training on the plasticity of cortical and subcortical neuronal populations.

AUTHOR CONTRIBUTIONS

Yonas Akalu and Dawson J. Kidgell conceptualized and designed the study. Yonas Akalu, Dawson J. Kidgell, Ummatul Siddique and Mohamad Rostami conducted the experiments, while Yonas Akalu, Dawson J. Kidgell, Patrick Vallance and Simon Walker analysed the data. The interpretation of findings was performed by Yonas Akalu, Dawson J. Kidgell and Simon Walker. Yonas Akalu, Ashlyn K. Frazer and Dawson J. Kidgell created the figures. Yonas Akalu and Dawson J. Kidgell drafted the manuscript. The manuscript was further reviewed and edited by Yonas Akalu, Jamie Tallent, Ashlyn K. Frazer, Ummatul Siddique, Mohamad Rostami, Patrick Vallance, Glyn Howatson, Simon Walker and Dawson J. Kidgell. Finally, all authors: Yonas Akalu, Jamie Tallent, Ashlyn K. Frazer, Ummatul Siddique, Mohamad Rostami, Patrick Vallance, Glyn Howatson, Simon Walker and Dawson J. Kidgell approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors do not declare any conflicts of interest.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/ejn.16297>.

DATA AVAILABILITY STATEMENT

Data for the experiments reported here can be made available upon reasonable request.

ORCID

Dawson J. Kidgell  <https://orcid.org/0000-0002-1800-382X>

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