EFFECT OF SHORT-TERM RESISTANCE TRAINING ON CORTICOSPINAL AND RETICULOSPINAL EXCITABILITY IN BICEPS BRACHII

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ABSTRACT

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BACKGROUND: Descending pathways, such as the corticospinal (CST) and reticulospinal tracts (RST), are highly influential structures that mediate movement. Although the two tracts have differences in their motor function (Lemon 2008), it has been postulated that both may contribute to neural adaptations to short-term resistance training (Siddique et al. 2020; Glover & Baker 2020). Studies using transcranial magnetic stimulation (TMS), a non-invasive form of brain stimulation, to measure intracortical and CST adaptations to resistance training have yielded equivocal results (Siddique et al. 2020). The effect of resistance training on RST excitability has yet to be investigated in humans. Therefore, the aim of this study was to measure adaptations of the CST and RST to a 6-week resistance training program. Two forms of resistance training (explosive and sustained contractions) were implemented to ascertain whether motor pathway adaptations are modulated by training type.

METHODS: Thirteen healthy young males were recruited and distributed into 3 groups: control (n = 5), explosive-contraction training (n = 4), and sustained-contraction training (n = 4). The 6-week at-home resistance training programs were conducted with a novel device that measured force production from isometric elbow flexion. Maximal strength was quantified by maximal voluntary contractions (MVCs) and explosive strength by rate of force development (RFD). Corticospinal adaptations were assessed by posterior-anterior (PA) current-induced motor evoked potential (MEP) amplitude, MEP latency, cortical silent period, and recruitment curve. Reticulospinal adaptations were measured using the StartReact test, loud acoustic stimulation (LAS) paired with TMS, and MEPs induced by anterior-posterior (AP) current orientation. Paired-sample t-tests were used for within-subject comparison to detect changes after the resistance training program. The alpha level of 0.05 was adjusted to $\alpha = 0.016$ to account for multiple comparisons.

RESULTS: Strength assessments did not yield significant changes in MVC or RFD in any group. Significant StartReact effects were observed across groups in both experimental sessions ($p = 0.001$), but there were no changes in the effect after training. Significant changes were not observed in MEP parameters for any group. No changes were observed in MEP suppression from the LAS paired with TMS protocol in any group, but MEP suppression occurred in the majority of participants in both experimental sessions (pre-intervention: 66.7%, post-intervention: 72.7%).

CONCLUSION: The lack of significant improvements in MVC or RFD in either training group indicates that the resistance training programs were not effective. It is also possible that small sample sizes limited statistical power, masking increases in MVC and RFD comparable to other resistance training studies. There were negligible changes in neural measures, and therefore, modulation of CST or RST excitability cannot be concluded. Baseline data from the neurophysiological tests were similar to previous studies, which substantiates the validity of these tests. Therefore, it is likely that the minimal observed neural adaptations are likely due to a lack of changes in neural function, rather than limitations in neural assessments.

Key words: reticulospinal, corticospinal, resistance training, TMS

ABBREVIATIONS

aMT	active motor threshold
AP	anterior-posterior
CNS	central nervous system
cSP	cortical silent period
CST	corticospinal tract
EMG	electromyography
ICF	intracortical facilitation
ISI	interstimulus interval
LAS	loud acoustic stimulation
M1	primary motor cortex
MEP	motor evoked potential
M_{max}	maximal compound action potential
MVC	maximal voluntary contraction
PA	posterior-anterior
RFD	rate of force development
RST	reticulospinal tract
SD	standard deviation
SICI	short-interval cortical inhibition
TMS	transcranial magnetic stimulation
VRT	visual reaction time
VART	visual-auditory reaction time
VSRT	visual + startle reaction time

CONTENTS

1 INTRODUCTION

The nervous system plays a central role in movement, with spinal tracts being a crucial component of the motor pathway by relaying signals towards the periphery. The corticospinal tract (CST) and reticulospinal tract (RST) are two notable descending pathways, originating in the cortex and brainstem, respectively (Lemon 2008). The CST has been coined as the primary motor pathway for its vital contributions to fine motor control and fractionated movements (Lawrence & Kuypers 1968a). Neuroscientists have historically emphasized that the RST provides gross motor, postural, and locomotive function (Buford 2009). Animal and human models have recently provided evidence for RST motor outputs to more distal muscles than was previously noted (Baker 2011; Akalu et al. 2023). Although humans still primarily rely on the CST for fine motor movements, the RST has the capacity for distal upper-extremity function as well.

The appreciation of more versatile contributions from the RST to force production has prompted investigations into the tract's role in resistance training (Atkinson et al. 2022). The benefits of resistance training for performance and longevity of functional capacity are well-appreciated (Kraemer et al. 2002). Acute responses and short-term adaptations of intracortical and corticospinal circuits to resistance training have primarily been assessed using transcranial magnetic stimulation (TMS), a non-invasive form of brain stimulation (Mason et al. 2018; Siddique et al. 2020). Implementation of single- and paired-pulse TMS protocols have yielded equivocal findings in terms of the location(s) and mechanism(s) of adaptation. Reticulospinal adaptations to resistance training have been observed in macaque monkeys (Glover & Baker 2020), but there is currently a lack of human evidence. The present study conducted a resistance training intervention to ascertain the modulatory effects on corticospinal and reticulospinal excitability.

2 CORTICOSPINAL AND RETICULOSPINAL MOTOR PATHWAYS

The nervous system is an essential component of movement containing many neural tracts, which transport motor commands from the brain and spinal cord to muscles (Figure 1; Lemon 2008). The two main pathways of interest for this thesis are the CST and RST. These spinal tracts consist of neurons projecting from their origins in the cortex and brainstem, respectively. Circuits in the brain and spinal cord that contribute to functionality of the CST and RST, as well as peripheral motor neuron function, are highly influential in motor outputs. The culmination of outputs from motor circuits dictates neural drive, enabling muscle contraction for movement.

2.1 Corticospinal tract

The CST is a collection of nerve fibers, which originate in the cortex (e.g., primary motor, premotor, supplementary motor, cingulate motor, and sensorimotor cortices) and project to the spinal cord to innervate spinal motor neurons (Figure 1; Lemon 2008; Kuypers 1981; Dum & Strick 2005). A small portion of CST neurons (~ 10%) have ipsilateral projections and the remaining axons decussate in the pyramids of the brainstem for contralateral motor control (Lacroix et al. 2004; Galea & Darian-Smith 1997). Corticospinal neurons primarily terminate in the spinal cord on their descending side, but it has been speculated that a small portion of corticospinal neurons decussate in the spinal cord at the level of motor neuronal innervation (Galea & Darian-Smith 1997). The CST has monosynaptic pathways conducting excitatory signals from the primary motor cortex (M1) to motor neurons (Bernhard & Bohm 1954; Palmer & Ashby 1992). The CST also has polysynaptic connections to motor neurons in the spinal cord via interneurons. Spinal interneurons integrate local inhibitory synapses with both excitatory and inhibitory inputs from descending and sensorimotor pathways (Lemon 2008). Increased CST excitation, dampened inhibition, or a combination of the two would augment cortico-motoneuronal outputs. As neural drive from the CST increases, motor neurons are more readily activated and muscle fibers contract. The balance of excitatory and inhibitory signals is important for limiting muscle inputs to those that contribute to coordinated movement.

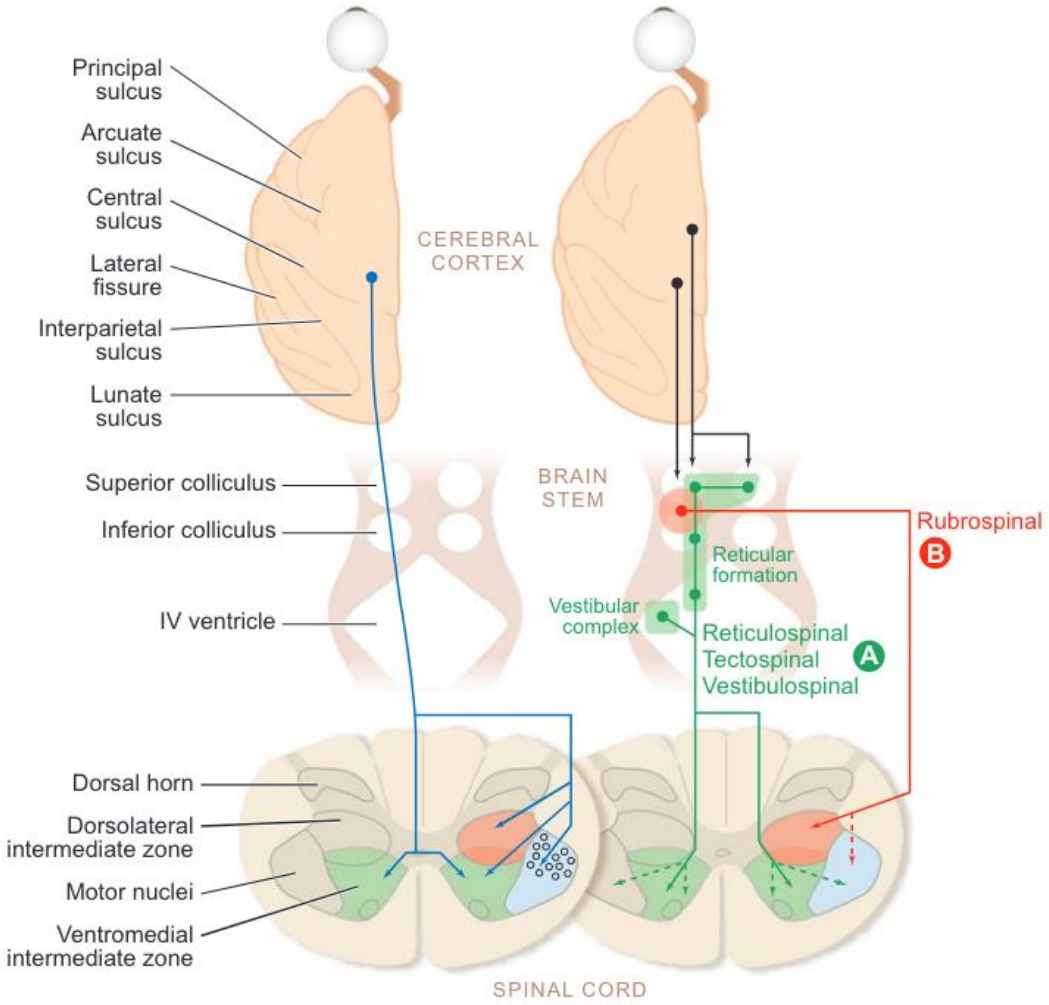

FIGURE 1. Simplified illustration of the descending spinal tracts. The corticospinal tract is displayed on the left in blue. Note that the blue zone with black circles indicates the region of motor neuron cell bodies. On the right, brainstem tracts are separated into two groups based on their spinal targets: ventromedial (A) and dorsolateral (B). The reticulospinal tract is depicted in green projecting bilaterally from the reticular formation to the ventromedial zone of the spinal cord. Dashed lines indicate branches with fewer fibers (Lemon 2008).

The CST is often considered the primary motor pathway based on its multifunctionality and direct connection from M1 to motor neurons. The many cortical origins of the CST and its terminations along the entire spinal cord contribute to its versatile motor function (Lemon 2008). The CST is well-known for its regulation of fractionated movements and fine motor control. A pivotal study by Lawrence & Kuypers (1968a) highlighted the CST's influence on hand muscles. The research team lesioned the CST in macaque monkeys to impair hand function. Some gross motor function was restored over time, but they never regained fine, independent finger

movements. Additionally, the CST provides input to reflexes and locomotive circuits in the spinal cord (Lemon 2008; Drew et al. 2004).

2.2 Reticulospinal tract

The RST refers to the entire motor pathway from the reticular formation to its terminations in the spinal cord (Figure 1; Lemon 2008). The reticular formation is composed of clusters of nuclei located deep and medial in the brainstem, spanning from the thalamus to the cervical spinal cord (Kuypers 1981; Lemon 2008). The main origin of the RST is the medial pontomedullary reticular formation (Peterson 1979). From nuclei of the reticular formation, the RST projects to spinal motor neuron pools with monosynaptic and oligosynaptic connections to motor neurons (Peterson 1979; Lemon 2008). Invasive animal studies have found that stimulation of reticulospinal neurons causes bilateral motor activation (Jankowska et al. 2003; Davidson & Buford 2006; Davidson et al. 2007; Schepens & Drew 2006). The two most common spinal tract divisions are the medial and lateral RSTs. The medial RST is located in the ventromedial funiculus, and the lateral RST resides in the ventrolateral and dorsolateral funiculi (Peterson 1979).

The versatile inputs to the reticulospinal system, and bilateral signal propagation of the RST, contribute to its role in coordinated whole-body movements (Buford 2009). Motor nuclei of the reticular formation mediate an extensive network of input signals to form appropriate motor outputs. The majority of cortical inputs are from M1 and premotor cortices, which synapse directly on reticulospinal neurons. Some cortico-reticular inputs are branches from corticospinal neurons, while others solely project to the brainstem. Cerebellar influence from the fastigial nucleus heavily modulates motor outputs from the reticulospinal system. Bilateral somatosensory inputs, especially those from proprioceptors (i.e., muscle spindles and Golgi tendon organs), also terminate on reticulospinal neurons (Buford 2009). The reticulospinal system uses input from sensory pathways (Drew et al. 1996) and the cerebellum (Mori et al. 2000) to induce feedback responses that inhibit postural instability, and feedforward adjustments for postural control and balance (Drew et al. 2004).

The most widely accepted functions of the RST are locomotion, posture, and gross motor movements (Buford 2009; Drew et al. 2004). Bilateral outputs from the RST create synergistic activation of ipsilateral flexor muscles and reciprocal inhibition of extensors, potentially with a

crossed extensor response activating contralateral extensors and inhibiting flexors (Davidson et al. 2007). Many studies on animals have displayed these locomotive and postural functions. Early studies stimulating the pontomedullary reticular formation in cats revealed ipsilateral and contralateral activation of the neck, back, and limb muscles (Peterson 1979). Prentice & Drew (2001) monitored neurons in the pontomedullary reticular formation in cats and found increased activity in most cells during a locomotive task. Significantly greater activation of the pontomedullary reticular formation was exhibited during trained reaching tasks on both the right and left side, simultaneously displaying the RSTs role in gross motor movements (reaching) and postural control (Schepens & Drew 2006). Further evidence for locomotive functioning were found via neurochemical modulation of the reticular formation, and lesions in the pontomedullary reticular formation that mainly impaired locomotion in cats (Buford 2009).

Reticulospinal functions have been considered distinct from the CST. A foundational contribution to our understanding of RST functioning relative to the CST was conducted by Lawrence & Kuypers (1968a; 1968b). In the same previously discussed sample of macaque monkeys with damaged CSTs, the reticulospinal and vestibulospinal tracts were lesioned. The result was impaired gross motor movements. Although these studies by Lawrence & Kuypers (1968a; 1968b) provided invaluable data, fine and gross motor function are not two distinct systems, but rather, motor pathways overlapping in their functions. Just as the CST has distal locomotive outputs, there is evidence for more distal RST influence via direct motor neuron terminals (Lemon et al. 2004). Motor neuron recordings using indwelling electrodes have revealed RST connections to the upper arm, forearm, and hand (Riddle et al. 2009). Functionally, the RST may be involved in hand grasping motions (Honeycutt et al. 2013). Although Honeycutt et al. (2013) failed to demonstrate RST activation during a finger movement task, activation observed during a hand grip task revealed a greater influence on distal motor movements than was previously appreciated. These studies exhibit progress in our understanding of reticulospinal function. However, our existing knowledge is still superficial and further research, especially in humans, is required to hone the extent of RST contribution movement.

2.3 Spinal and peripheral contributors to movement

Motor commands from descending pathways, such as the CST and RST, must consolidate before reaching muscle fibers. The final neural input to muscle is the alpha (α-) motor neuron, which projects from the ventral horn of the spinal cord to innervate skeletal muscle fibers. An α-motor

neuron and the group of muscle fibers it innervates is known as a motor unit (Enoka 2008, 198). In its simplest form, an α-motor neuron is excited by a collection of spinal neurons to an extent that supersedes its activation threshold, causing the muscle fibers of that motor unit contract. The reality is far more multi-faceted with a variety of factors at play. The intricacies of spinal circuits, their inputs, and forms of α-motor neuron activation are all important factors in force production.

It is important to address inputs to spinal neurons and motor neurons. As previously discussed, descending motor commands from cortical and brainstem regions terminate on spinal circuits. The CST and RST contribute with mono- and oligosynaptic inputs to motor neurons (Lemon 2008). Therefore, both CST and RST neurons have direct and indirect influence on α-motor neurons. Somatosensory feedback from proprioceptors (i.e., muscle spindles and Golgi tendon organs) is also essential for executing necessary adjustments to force production (Enoka 2008, 272). One mechanism used by the CST and RST to implement locomotive and postural commands is the modification of central pattern generators (CPGs) (Drew et al. 2004; Enoka 2008, 276-278). CPGs are automatic neural networks located in the brainstem and local circuits of the spinal cord that contribute to locomotion by creating bilateral motor patterns. These pre-existing networks store motor plans and contribute to efficient execution of frequently utilized movements. CPGs can function independently from descending motor pathways or are modulated by the CST and RST when alterations are necessary (Enoka 2008, 276-278). This small glimpse into the components and mechanisms of spinal circuits can help explain the final output from motor neurons, but our current understanding is quite superficial and constantly evolving.

The net effect of inputs on α-motor neurons determines whether the neuron will be activated to induce a contraction. Input from descending tracts, somatosensory input, and local spinal networks terminate on α-motor neurons with excitatory (EPSP) and inhibitory post-synaptic potentials (IPSP) to modulate activation of muscle fibers, and the summation of those potentials dictates neural drive. Spatial and temporal summation of EPSPs and IPSPs determine whether the activation threshold of a motor neuron will be reached (Enoka 2008, 192).

The specificity of motor unit activation (type and size of recruited motor units) is highly influential in the resulting contraction and profile of force production. Perhaps the most influential effectors of α-motor neuron recruitment, and subsequent force production, are motor unit type, size, and firing rate. The three types of motor units – slow (Type I), fast fatigue-resistant

(Type IIa), and fast fatigable (Type IIx) – all have distinct patterns of force production, as described by their names (Burke 1967). Motor neuron recruitment begins with the smallest motor units and continues with increasing size (Henneman et al. 1965). Recruitment order also coincides with motor unit type. Less fatigable slow-twitch units (Type I) are recruited first, followed by fast-twitch units (Type IIa), and finally the most fatigable fast-twitch units (Type IIx). This consistent recruitment order is likely due to lower activation thresholds for small motor units and higher thresholds for larger units (Henneman 1957). Firing rate, or the frequency of signal propagation along the α-motor neuron's axon, is also an important regulator of motor commands. In rapid voluntary contractions, for example, most motor units are recruited at the beginning (first 35 ms) of electromyography (EMG) activity and firing rates usually peak in this time period (Del Vecchio et al. 2019). The association between firing rate and force production indicates that neural drive predominantly occurs before, and at the beginning of, force production to produce an explosive contraction > 75% of maximum voluntary force. While motor unit recruitment order may be consistent, firing rate is dependent on properties of the contraction (e.g., speed, duration, intensity).

3 NON-INVASIVE ASSESSMENTS OF MOTOR PATHWAYS

There are multiple non-invasive methods to investigate corticospinal and intracortical function via direct and indirect neuronal stimulation (e.g., transcranial magnetic stimulation, transcranial electrical stimulation, transcranial direct-current stimulation) (Di Lazzaro & Rothwell 2014). Artificial stimulation and functional assessments of the reticular formation, however, are especially challenging to implement non-invasively given the deep and dispersed anatomy of motor nuclei in the brainstem. Nonhuman primate studies have been essential to our understanding of RST contributions to motor function by implementing invasive measures of RST activity, which directly stimulate and measure output from reticular neurons (Baker 2011). Notably, the field is lacking in human-based investigations of the RST. The purpose of this section is to address the existing methods for measuring CST and RST excitability in humans through non-invasive stimulation techniques.

3.1 Transcranial magnetic stimulation

TMS is a non-invasive and painless form of brain stimulation originally conceived for cortical excitation in healthy individuals and diagnostics (Barker et al. 1985). TMS is a highly valuable tool for mechanistic investigations because its manipulation of the nervous system allows for studies to deduce causation based on EMG responses. TMS also has a variety of applications depending on the target of stimulation (Rossini et al. 2015). When used to stimulate the motor cortex, TMS can be an effective tool for investigating motor function and excitability of descending pathways, including the CST and RST (Chen 2000; Di Lazzaro & Rothwell 2014; Fisher et al. 2012).

3.1.1 Mechanisms of stimulation-induced neural activation

A TMS device consists of a central machine and a stimulation coil (Epstein 2008). The machine stores power in capacitors and engaging the trigger causes energy transfer to wires within the coil. TMS relies on the principles of electromagnetic induction – the generation of an electrical current in a conductor, i.e., brain tissue, from changes in a magnetic field (Epstein 2008). With each pulse, a transient electrical current in the coil generates a magnetic field, or flux, perpendicular to the coil (Figure 2; Hallett 2007). When the coil is placed near the head, the magnetic field penetrates the scalp and skull (Epstein 2008). Changes in the magnetic field from

a TMS pulse induce an electrical field within the brain, which according to Lenz's law, is parallel and opposite to the original coil current. As a result, the electrical current depolarizes neurons in its path. Increased rate of change in the magnetic field augments the magnitude of the electric field and its current induced in the brain, which causes greater neuronal activation in a larger cortical region (Epstein 2008). The net effect can be excitatory or inhibitory depending on the cortical regions and synapses that are activated (Hallett 2007; Kobayashi & Pascual-Leone 2003). This underlying electromagnetic mechanism is what makes TMS a non-invasive method for neural stimulation.

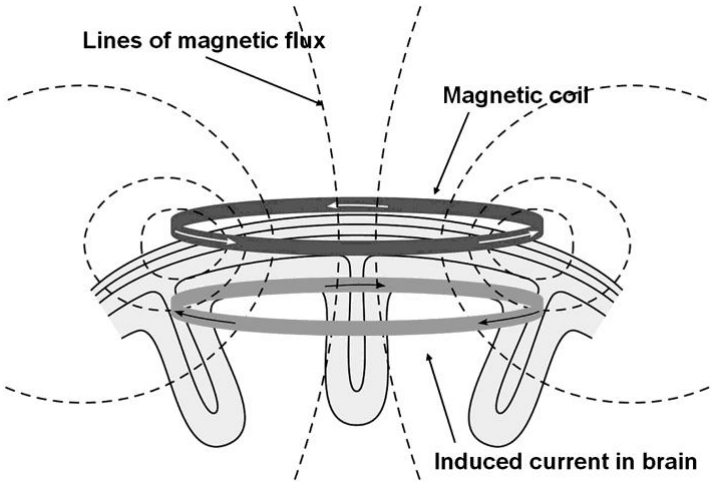

FIGURE 2. Illustration of electrical current flow direction in a round stimulation coil, the resulting magnetic field, and the current induced in the brain (Hallett 2007).

The coil shape determines the shape of the magnetic field, which ultimately dictates the area and magnitude of stimulation. The most common coil formations are round, figure-of-eight, and double-cone. The traditional round coil provides more dispersed stimulation through a circular current flow (Hallett 2007). Its strongest currents are near the circumference of the coil with no current at the center. The figure-of-eight coil provides more focal stimulation as it forms a peak current at the center of the coil (Hallett 2007). The double-cone coil induces deeper stimulation, often more suitable for lower extremity muscles (Groppa et al. 2012). Even the most focal figure-of-eight coil will stimulate neighboring neurons to the target cortical region and cause transsynaptic dispersion of signals to more distant cortices. For example, Di Lazzaro et al. (1999) and Ferbert et al. (1992) found stimulation of the M1 hand region inhibited the contralateral M1 hand region at higher stimulation intensities (> 55% maximum stimulator output). The most pronounced EMG responses to TMS have been observed when the coil induces a posterior-

anterior (PA) directed current in the brain; coil orientation must be at 45° from the mid-sagittal line with the handle directed caudally for PA current (Mills et al. 1992; Reijonen et al. 2020).

Direct neuronal activation is dependent on the extent of axonal depolarization – outward transmembrane ion flow. Neurons located nearest the strongest induced electrical currents, which is also where the rate of change in the magnetic field is the greatest, are the most likely to reach their threshold for an action potential (Groppa et al. 2012). Superficial cerebral regions of both gyri and sulci are readily activated (Fox et al. 2004), but gyral regions are exposed to the strongest electrical fields (Siebner et al. 2022). Stimulation of cortical neurons is thought to mainly occur along the axon due to a lower excitation threshold than the cell soma (Nowak & Bullier 1998). The axon terminal is a proposed primary site of activation. A TMS-induced current parallel to the distal end of an axon and directed toward the terminal causes depolarization (Figure 3). Reversing the direction of the current by turning the coil 180° would activate axonal branches extending in the opposite direction (Aberra et al. 2018; Siebner et al. 2022). The curvature of the axon relative to the induced current also impacts membrane depolarization. Maccabee et al. (1993) found *in vitro* mammalian neurons were more susceptible to depolarization as the angle of a bent axon increased when the induced current was directed parallel to the flat portion of the axon. These studies speculated that activation most likely occurs at the axon terminal, and possibly at bends in the axon, but it is possible there are alternative sites or conditions susceptible to TMS-induced activation yet to be determined.

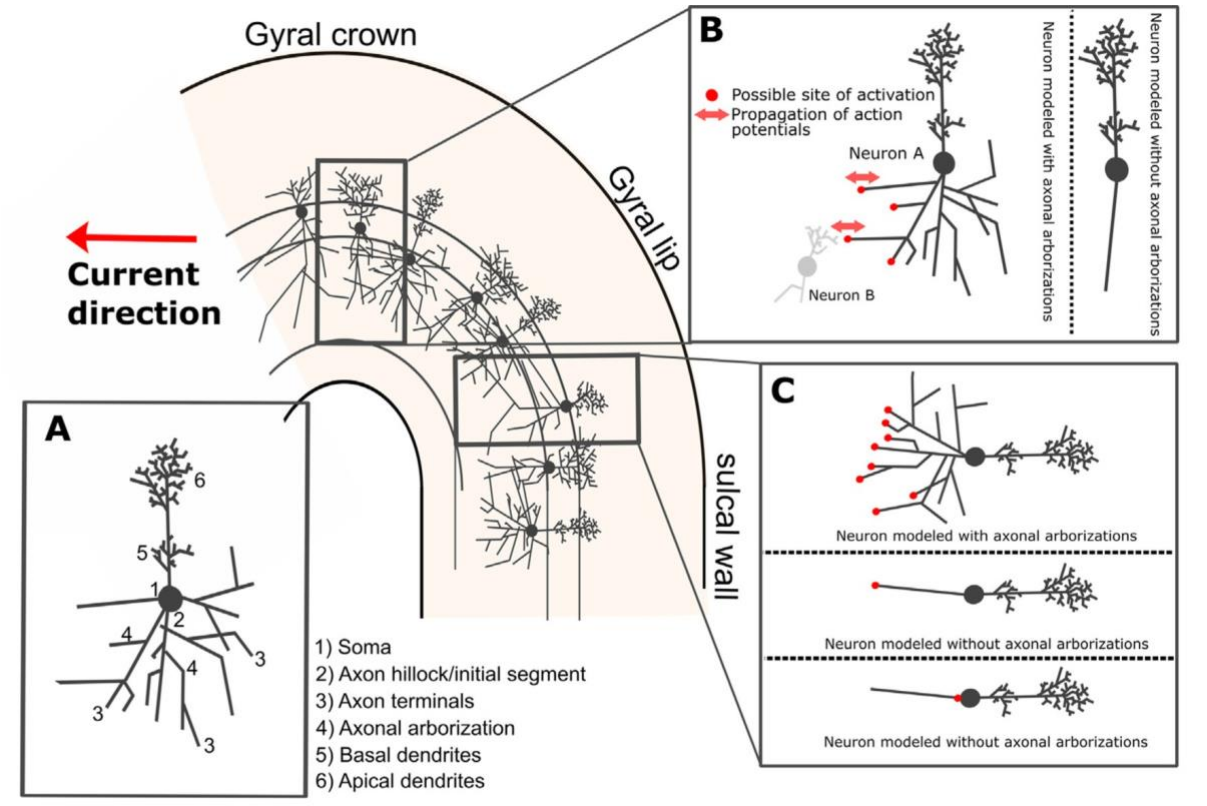

FIGURE 3. Axon activation sites relative to TMS-induced electrical current direction. Theoretical neurons are depicted in a sagittal view of motor cortex layers II and III. (A) Anatomical diagram of a typical pyramidal neuron. (B) Two depictions of a neuron in the gyral crown, one with arborizations (branching) and another without. The neuron with arborizations has multiple activated terminals (red), and signal propagation occurs both orthodromically and antidromically. The neuron without arborizations only extends ventrally so activation is less likely. (C) Three depictions of the same neuron in the sulcal wall, one with arborizations and two without. Activation sites are found at the axon terminal and many of its collaterals. Although less likely, the axon hillock is also a possible site for activation in this orientation (Siebner et al. 2022).

Action potentials directly triggered by a TMS-induced current that propogate orthodromically can activate other cortical neurons transsynaptically, including corticospinal neurons in M1. Investigations into the timing of signals carried by spinal tracts, also known as descending volleys, have provided insight into the intracortical activation mechanisms of TMS. Direct-waves (D-waves) are volleys caused by the direct stimulation of corticospinal neurons by TMS, and indirect-waves (I-waves) are volleys induced by indirect corticospinal activation via cortico-cortical pathways (Patton & Amassian 1954). The volley types can be identified by their latencies. Transsynaptic delays cause I-waves to have a longer latency than D-waves, but the

timing of those latencies depends on the level of recording (Figure 4a; Di Lazzaro et al. 2004). Day et al. (1989) used surface and needle EMG recordings of the first dorsal inerosseous muscle to compare the inferred descending volleys from TMS to those from transcranial electrical stimulation (TES) and found TMS-induced volleys were primarily I-waves. These findings were supported by intraoperative cervical and thoracic spinal recordings in anesthatized humans, and greater TMS intensities were found to induce D-waves (Burke et al. 1993; Thompson et al. 1991). Therefore, corticospinal neurons are most often excited though cortico-cortical pathways, but high-intensity TMS may provoke direct neuronal stimulation. Temporal and spatial summation of descending volleys, and their oligosynaptic connections, on an α-motor neuron that surpases its activation threshold will cause a contraction in the innervated muscle (Groppa et al. 2012).

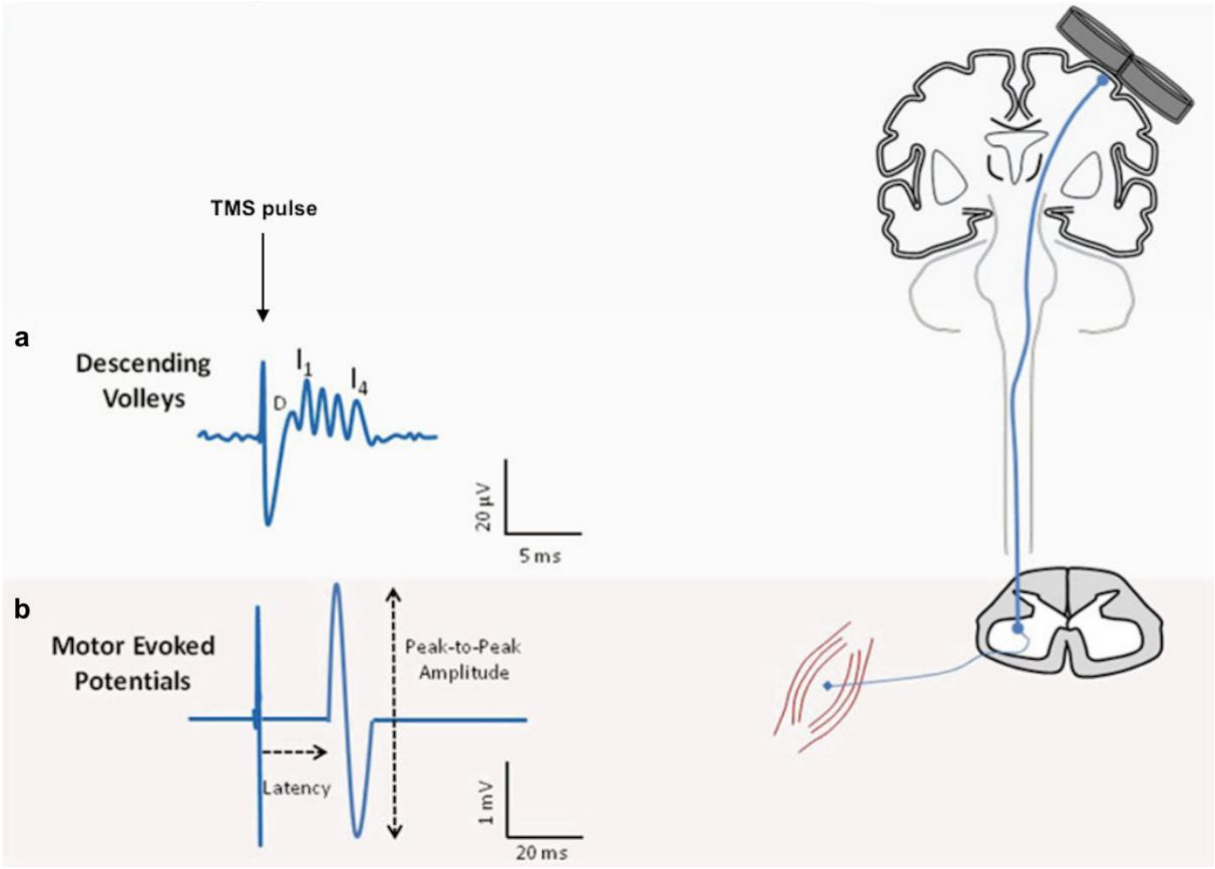

FIGURE 4. Diagram of TMS-induced potentials at the spinal (A) and muscle level (B). Descending volleys are signals recorded from spinal tract neurons. Motor evoked potentials (MEPs) are EMG recordings from the target muscle caused by α-motor neuron activation. Modified from Farzan (2014).

3.1.2 Intracortical and corticospinal assessments

Motor responses to TMS are most commonly measured peripherally through surface EMG signals (Barker et al. 1985). Recording electrical activity from target muscles enables assessment of motor pathway excitability and inhibitory circuits. Motor evoked potentials (MEPs) are the most fundamental measure, representing the muscle's electrical response to stimulation using EMG (Figure 4b; Kobayashi & Pascual-Leone 2003). MEP amplitude and latency are a quantification of cortico-motoneuronal excitability (Rossini et al. 2015). Amplitude can be defined as the peak-to-peak voltage (difference between the largest depolarization and hyperpolarization peaks) or the integral of a rectified MEP (Figure 4b). Greater MEP amplitudes at a constant stimulation intensity reflect greater neural excitability. MEP latency is the time from stimulation to MEP onset and shorter latencies indicate enhanced excitability (Rossini et al. 2015). Excitability of the motor pathway heightens during voluntary contraction of the target muscle as a result of increases in the number and magnitude of descending volleys (Di Lazzaro et al. 1998). An active state will also increase excitability in the spinal motor neuron pool and cause recruitment of more motor neurons, assuming that all external stimulation components (i.e., intensity, pulse type, location) are consistent (Groppa et al. 2012).

MEPs can then be used to calculate motor thresholds (MTs) – the lowest stimulation intensity that consistently evokes a MEP (Rossini et al. 2015). The MT represents membrane excitability and synaptic efficiency of neurons along the entire motor pathway. Administration of a Na^+ and Ca^{2+} channel blocker validated the importance of membrane excitability as the drug increased MTs (Ziemann et al. 1996a). The more excitable neuron membrane is more readily stimulated at lower intensities by its lower threshold for activation, yielding a lower MT. MTs are also helpful for identifying a normalized stimulation intensity in TMS protocols. MEP amplitudes are variable for any given intensity and the intensity sufficient to induce MEPs is highly individual. Therefore, stimulation intensities for a given protocol are often relative to the individual's MT. MTs can be reported at rest or during voluntary contraction depending on the stimulation protocol. For example, an active MT (aMT) is typically used when TMS is implemented while the target muscle is lightly contracted (Rossini et al. 2015; Farzan 2014).

Recruitment curves, or input-output curves, are another common excitability measure, reflecting how rapidly MEP amplitudes increase as a function of stimulation intensity (Devanne et al. 1997). In healthy individuals, recruitment curves have a sigmoidal shape and plateau after a

certain intensity where MEP amplitudes reach their maximum (Rossini et al. 2015). Recruitment curves are typically measured by increasing the stimulator output and repeating a series of stimulations at each increment. The initial intensity is often at the MT and intensity is increased in intervals relative to the MT. The slope of the curve and MEP amplitudes at the horizontal asymptote are the outcome measures. A steeper slope and higher MEP amplitudes at the asymptote are both indicative of augmented corticospinal excitability (Farzan 2014). Various studies have introduced neuromodulatory drugs to investigate the site(s) that effect recruitment curve outcome measures. Administration of a γ-aminobutyric acid (GABA) type A receptor positive allosteric modulator (lorazepam) caused significant attenuation of the slope and MEP amplitude at the asymptote (Boroojerdi et al. 2001). Dopaminergic-noradrenergic agonist (D-amphetamine) enhanced both variables (Boroojerdi et al. 2001). These findings indicate inhibitory (GABAergic) and excitatory (noradrenergic) neurotransmitters modulate both the slope and asymptote.

Another peripheral output measure of TMS is the silent period – a period of EMG suppression after the MEP observed while the participant is contracting. The measure is often termed cortical silent period (cSP) to emphasize the intracortical mechanisms behind the phenomenon (Wilson et al. 1993). The inhibitory mechanism is not fully understood, but administration of various $GABA_A$ and $GABA_B$ receptor-modulating drugs have indicated that the cSP is mediated by cortical and spinal GABA-ergic interneurons activated by TMS (Siebner et al. 1998; Werhahn et al. 1999; Pierantozzi et al. 2004). cSPs are known to increase in duration as stimulator output increases, and eventually plateau. The cSP can last upwards of 200 ms depending on the conditions (Kimiskidis et al. 2005). The initial ~ 50 ms is likely from spinal mechanisms, such as Renshaw cells (Fuhr et al. 1991), and the latter period is due to cortical inhibition (Inghilleri et al. 1993). A reduction in cSP duration would indicate dampened corticospinal inhibition. The measure on its own is limited in its ability to differentiate cortical and spinal influences.

TMS protocols can range from one stimulation to hundreds in succession (repetitive TMS; rTMS) depending on the application. Short exposure to small amounts of single-pulse TMS has transient effects, while a single session of rTMS can induce neuromodulatory effects lasting minutes to hours (Hallett 2007). Single-pulse protocols modulate the entire cortico-motoneuronal pathway with one isolated stimulation, thus detecting modifications at a specific level of the pathway is difficult. Alternative TMS methods, which were not implemented in this thesis, can be used to ascertain the level of influence in the cortico-motoneuronal pathway. Assessment of intracortical

connectivity can be achieved using sets of two pulses discharged in quick succession, known as paired-pulse TMS. Cortical inhibitory and facilitatory mechanisms can be demonstrated with short-interval cortical inhibition (SICI) or intracortical facilitation (ICF) (Kujirai et al. 1993; Ziemann et al. 1996b). Both protocols start with a subthreshold conditioning stimulus, followed by a suprathreshold test stimulus. The difference in inter-stimulus intervals (ISI) between the TMS pulses dictates the neuromodulatory effects of the protocol. SICI has a shorter ISI (1-6 ms) to induce inhibition and reduction of MEP amplitudes, while ICF has a longer ISI (~ 6-20 ms) for MEP facilitation (Kujirai et al. 1993; Ziemann et al. 1996b). The conditioning stimulus in SICI primarily activates low-threshold inhibitory cortical $GABA_A$ receptors, possibly down to specific receptor subtypes, causing suppression of the test stimulus MEP (Ziemann et al. 1996b; Di Lazzaro et al. 2007). ICF likely causes facilitation of I-waves which, as supported by a number of studies, is affected by multiple neurotransmitter circuits, e.g., GABA, dopamine, noradrenaline, and NMDA (Ziemann et al. 2015).

The test-retest reliability of TMS parameters is generally observed to be at an acceptable level in healthy individuals (intraclass correlation coefficients [ICCs] > 0.8; Atkinson & Nevill 1998). Peak-to-peak amplitude reliability has been reported at rest with ICC = 0.89 (Leung et al. 2018) and ICC = 0.88 (Cacchio et al. 2011), and with ICC = 0.830 during 10% maximal voluntary isometric contraction of the knee extensors (Leung et al. 2018). Better reliability has been reported for latencies (ICC = 0.95; Cacchio et al. 2011) and resting MTs (ICC = 0.97; Malcolm et al. 2006). Reliability data of cSPs were comparable to MEP amplitude (ICC = 0.87, Leung et al. 2018). Recruitment curve slopes have been especially unreliable with ICCs ranging from 0.60-0.83 depending on the target muscle within the hand and forearm (Malcolm et al. 2006). Proximal and distal muscles do not seem to differ in test-retest reliability of the measure. It is difficult to ascertain inter-rater reliability of TMS by comparing reliability studies due to the many stimulation methodologies and varying quality (Beaulieu et al. 2017).

MEP parameters should be reported as an average of many trials to account for the high inter-trial variability (Burke et al. 1995; Goldsworthy et al. 2016). There is evidence that external factors (to TMS) contribute to inter-trial variability, including oscillatory fluctuations in brain activity (Mitchell et al. 2007), state of arousal (Mars et al. 2007), alterations in voluntary muscle contraction (Kamen 2004; Darling et al. 2006), and external noise. Changes in EMG electrode placement, as well as the previously mentioned factors, could cause variability between experimental sessions. Even optimizing spatial precision of stimulation using navigated TMS

does not always improve MEP amplitude variability or reproducibility (Julkunen et al. 2009; Jung et al. 2010). It is possible to mitigate variability in TMS measures by keeping environmental factors as consistent as possible, avoiding factors of daily living that may alter neuropsychological state (e.g., caffeine, sleep deprivation, stress), providing the participant with force feedback to maintain EMG signals (Nielsen 1996), and increasing the number of trials. Goldsworthy et al. (2016) found that 20-30 trials are needed to achieve acceptable within-subject MEP amplitude reliability, and further improvement in reliability was not observed beyond 30 trials.

3.1.3 Reticulospinal assessments

M1 is the most common target for TMS assessments of motor pathway excitability. The previously mentioned response measures – MEP amplitude, MEP latency, recruitment curve, and cSP – are all assessments of the cortico-motoneuronal pathway. Motor nuclei in the reticular formation are subcortical, and therefore, direct stimulation would require invasive methods. Until recently, researchers have been reluctant to assume that excitability measures from cortical stimulation reflect RST excitability. Investigations observing brainstem activity in monkeys have provided support for TMS-induced activation of the cortico-reticular pathway. Fisher et al. (2012) hypothesized that TMS applied to M1 in macaque monkeys would indirectly stimulate the motor nuclei of the pontomedullary reticular formation via cortico-reticular neurons. The researchers observed threshold intensity for reticular cell activation decreased as latency increased (early: 1-3 ms, mean threshold = 71%; middle: 3-7 ms, mean threshold = 68%; late: 7-25 ms, mean threshold = 55%), which indicates the existence of multiple cortico-reticular pathways. The authors proposed that the only plausible cause for latencies < 3 ms are monosynaptic connections stimulated by TMS. Activation of cortico-reticular pathways with TMS cannot be validated in humans because it requires the use of indwelling electrodes in the brainstem to record neural activity. However, the authors claim that these findings in nonhuman primates could reflect human neurophysiology (Fisher et al. 2012).

Now that there is evidence for TMS-induced cortico-reticular neuron activation, researchers are determining the most effective protocols to stimulate these circuits. Cortico-reticular pathways may be more susceptible to activation in the anterior-posterior (AP) current direction (180° to the PA orientation) using a figure-of-eight coil. AP current stimulation evokes later I-waves with longer latencies than PA, which would indicate greater contributions from pathways with

multiple synapses or slower conduction velocities (Day et al. 1989; Di Lazzaro et al. 2001). This evidence could mean that while the PA current direction has predominantly CST influence, the AP induces both CST and RST activation. Therefore, comparing MEPs from PA and AP current directions could be a method for detecting changes in RST excitability. For example, a change in MEP amplitude and latency from AP current stimulation without changes in PA MEPs would imply reticulospinal adaptation (Germann & Baker 2021). The use of AP current stimulation to quantify RST excitability has not been validated in humans. The only known techniques for a validation study (i.e., indwelling electrodes in the brainstem) would be too invasive.

3.2 Auditory startle response

Startling auditory stimuli have been proposed as an alternative tool to activate motor nuclei in the reticular formation (Tapia et al. 2022). Initial studies on the startle reflex, evoked by unexpected loud acoustic stimulation (LAS), were conducted in a rested state and measured involuntary muscular responses with EMG recordings (Brown et al. 1991). These early investigations led to the postulation that subcortical structures are responsible for the startle response.

The auditory startle response has since been expanded from involuntary movements to planned motor tasks, which further support the theory of subcortical origins. There is evidence suggesting that by informing the participants of the motor task, their vestibular system primes the reticular formation to release the motor command upon stimulus onset (Carlsen et al. 2004). A response via the CST, originating in the cerebral cortex, would take longer than pathways with subcortical origins (Carlsen et al. 2003). In neurologically healthy humans, voluntary reaction times can shorten under more startling conditions when movements are pre-instructed, but not when the participant is allowed to choose the movement (Carlsen et al. 2004). It was postulated that choosing an action requires cortical input while pre-instructed actions are released subcortically. Therefore, the modulation of reaction times for only pre-instructed actions supports the theory that LAS induces reticular activation. EMG patterns also provide evidence for subcortical mechanisms (Valls-Solé et al. 1999). When given a task, the startle response induced an EMG onset with a shorter latency than that calculated for cerebral pathways. Additionally, EMG patterns did not exhibit voluntary activity, providing further evidence for reticulospinal activation from LAS over corticospinal activation (Valls-Solé et al. 1999).

The shortening of reaction times from more startling cues is known as the startle response (Valls-Solé et al. 1995), which can be assessed using a StartReact test. The StartReact test is implemented by first instructing the participant to perform a specific motor task in response to a light cue. The participant is exposed to auditory stimuli of varying intensities in a randomized order. The conditions are a visual stimulus alone, a visual cue with a quiet sound, and a visual cue with a loud sound (Figure 5). Valls-Solé et al. (1995) reported an optimal delay of 0-75 ms between visual and auditory stimuli, as all ISIs within this range yielded a significant reduction in reaction times compared to visual stimulus alone. Reaction times tended to increase with ISI (0 ms ISI: 79.7 ± 16.5 ms, 25 ms ISI: 102.9 ± 19.0 ms, 50 ms ISI: 114.2 ± 22.5 ms, 75 ms ISI: 121.5 ± 20.2 ms), but this was not substantiated with statistical analyses comparing ISI conditions (Valls-Solé et al. 1995).

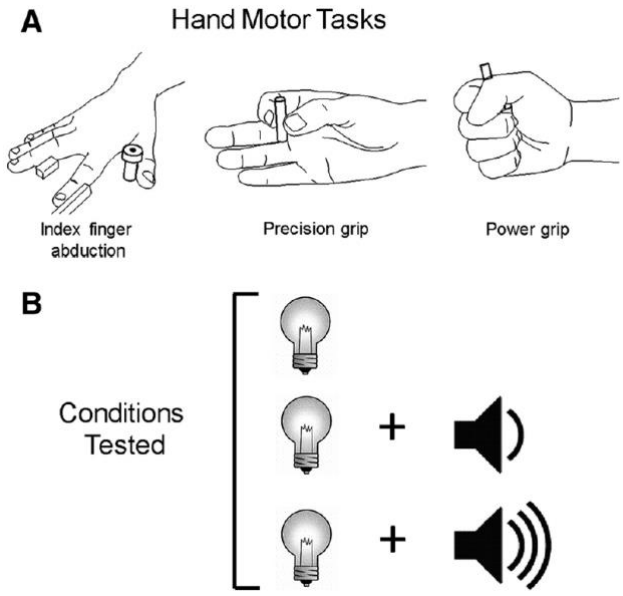

FIGURE 5. Example experimental setup of the StartReact test (Baker & Perez 2017). Participants completed index finger abduction, precision grip, and power grip. Their quiet acoustic stimulus was 80 dB (500 Hz, 20 ms) and loud acoustic stimulus was 115 dB. The combinations of motor tasks and stimulus condition volume can vary depending on the study.

Reaction times are defined as the duration from stimulus to EMG onset. The outcome of interest, the StartReact effect, is the difference between reaction times of the loud and quiet auditory conditions. Given that the startle response is thought to be induced by subcortical structures, a greater reduction in reaction time from quiet to loud sound conditions, or greater StartReact effect, indicates augmented reticulospinal excitability (Tapia et al. 2022).

The StartReact test has been implemented as an assessment tool of RST function in a variety of populations. Honeycutt et al. (2013) used the StartReact test to investigate which movements are modulated by RST function. Latency periods were shorter in a grasp task, while a finger task was not susceptible to the StartReact response, indicating that the RST plays a role in grasping but not necessarily fractionated finger movements. The StartReact test has also been used in clinical settings. Patients with reticular formation damage, like those with Parkinson's disease, have shown longer StartReact responses (Nonnekes et al. 2014). Spinal cord injury patients have exhibited more pronounced StartReact responses than healthy individuals (Baker & Perez 2017). The authors postulated that these findings are caused by enhanced RST excitability as the tract compensates for CST damage. Augmented RST functionality was only observed in the power grip task (Figure 5; Baker & Perez 2017), but that is to be expected given the presumed integration of corticospinal neurons on such distal muscles (Carlsen et al. 2009).

Neurophysiologists follow the assumption that the StartReact test measures excitability of the RST, but it does not mean that the test exclusively captures the RST in humans. Studies verifying the exclusion of CST activation have not been conducted in humans. It is also possible that StartReact responses could be confused with the involuntary startle reflex, however unlikely given that these voluntary actions have longer reaction times. For example, voluntary finger abduction reaction time to a startling sound (mean: 115 ± 35 ms; Baker & Perez 2017) has shown to be longer than the startle reflex in the first dorsal interosseous muscle (median reflex latency: 76.2 ms, range: 71.7-175.5 ms; Brown et al. 1991). There is convincing nonhuman primate data validating the method's sole activation of the RST (Tapia et al. 2022), but validation studies in humans are lacking.

The startle response has also been combined with TMS to assess reticulospinal excitability. The same theory that LAS activates subcortical structures can be applied. Exposing a participant to a LAS prior to the TMS stimulation (LAS + TMS) causes MEP suppression (Figure 6; Furubayashi et al. 2000). It has been postulated that LAS exposure causes cortical suppression via reticular formation activation (Germann & Baker 2021). Therefore, increased MEP suppression from the LAS + TMS protocol would indicate increased RST excitability. Similar to the previously mentioned assessments of RST excitability, the neurophysiological mechanisms underpinning the method are mainly speculative and have not been validated in humans.

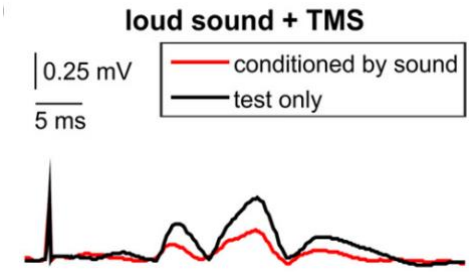

FIGURE 6. Rectified MEPs induced by TMS alone (test only) and LAS + TMS (conditioned by sound) (Germann & Baker 2021).

Auditory mechanisms of reticulospinal activation have also been used to induce RST plasticity. Fisher et al. (2012) suggested that high-intensity clicks from the TMS coil might activate the vestibular system and excite the RST. Click stimuli given in the same position as a TMS coil, using a bone vibrator, induced latency responses and spike patterns similar to TMS-induced reticular cell activity. Initial attempts have been made to implement auditory stimulation in humans for RST facilitation. Foysal et al. (2016) created a device that paired auditory clicks with biceps stimulation. The device was worn for a 6-hour period while participants engaged in typical daily tasks. Those exposed to paired stimulation had improved StartReact responses, which indicates that the paired auditory and peripheral electrical stimulations induced plasticity in the reticulospinal system (Germann & Baker 2021). Following the neuroplastic effects found from auditory and peripheral electrical stimulation, Germann et al. (2023) sought to determine whether LAS + TMS could induce plasticity in the reticulospinal system. MEP facilitation was found in the LAS + TMS condition 10, 20, and 30 min after stimulation. Not only is LAS + TMS likely an assessment of the RST, but it can have longer-lasting effects (Germann et al. 2023).

4 NEURAL ADAPTATIONS TO RESISTANCE TRAINING

Resistance training is beneficial for mobility and quality of life by increasing muscular strength (Ratamess et al. 2009). A resistance training program can be manipulated to achieve specific strength and performance outcomes. Modifiable variables include: muscle action (e.g., eccentric, concentric, isometric), resistance or load intensity, volume (sets and repetitions in one session), working muscles, contraction velocity, and training frequency (sessions per week) (Kraemer & Ratamess 2004). A training program can also be progressive – a systematic increase of the workload – to continually increase strength gains. Once an individual adapts to an initial stimulus, progressive overload is necessary for further improvements (Kraemer & Ratamess 2004). In an experimental context, this can be accounted for by using a resistance relative to one's maximum voluntary contraction (MVC). As physiological adaptations improve strength in the supercompensation phase after training (Bompa & Buzzichelli 2019), resistance can be increased in a standardized manner.

Based on the law of specificity, these variables are altered to obtain different phenotypes. For example, explosive strength can be trained with power loading (medium volume: 4-10 repetitions/set, low-moderate load: 30-70% of one-repetition maximum [1RM]; Häkkinen et al. 1985), maximal strength can be improved with high load and low volume ($\geq$ 80% of 1RM, 1-6 repetitions/set; Latella et al. 2017), and hypertrophy can be achieved with low-moderate load and high volume (67-75% of 1RM, 6-15 repetitions/set; Ratamess et al. 2009). Motor pathway adaptations could vary between training types to induce these different phenotypes, although, the field is currently limited by a lack of mechanistic data.

Both neural and muscular adaptations augment maximal force production and are essential contributors to strength gains (Sale 1988). Early adaptations contributing to increased strength from resistance training are thought to be predominantly neural (Moritani & deVries 1979), but the specific mechanisms have yet to be determined. Numerous effectors on force production at the cortical, subcortical, spinal, and motor neuronal levels create vast possibilities of mechanistic sources for neural adaptations to resistance training.

The relative contributions of the CST and RST to force production, and their plasticity in response to a resistance training program, have yet to be determined in humans. TMS has been an essential tool for assessing modulation of motor pathways by resistance training interventions.

The intracortical and upper motoneuronal mechanistic insights from TMS make it a far more useful method for assessing motor pathway adaptation than EMG alone (Farina et al. 2014). Therefore, this section will use TMS response measures to interrogate acute neural responses and short-term adaptations to resistance training. Changes in excitatory and inhibitory synapses have been found acutely (after one training session) and after short-term resistance training programs (a few weeks). TMS has only been used to address intracortical and corticospinal adaptations to resistance training (Atkinson et al. 2022; Mason et al. 2018; Siddique et al. 2020). Reticulospinal adaptation has yet to be investigated in humans.

4.1 Acute neural responses to resistance training

Several studies have measured plasticity of intracortical and corticospinal neurons after a single resistance training session with inconsistent results. A meta-analysis of nine articles found that stimulation within one hour of training yielded greater MEP amplitudes, but heterogeneity within the data was high (Mason et al. 2018). Different types of resistance training (e.g., maximal strength, hypertrophic, ballistic) had to be grouped together in the meta-analysis for adequate sample sizes, possibly masking training type-specific neural responses and contributing to variance in the data. Studies have found decreased (Latella et al. 2016) and increased (Leung et al. 2015; Latella et al. 2017; Nuzzo et al. 2016) MEP amplitudes immediately post-training. MEP responses also changed depending on the measurement time after training. Latella et al. (2016) observed MEP suppression immediately post-training, then no change until facilitation at 72 hours. Even within the same study, changes in MEP amplitude differed between resistance training types. Leung et al. (2015) observed increased MEP amplitudes in metronome-paced and visuomotor skill training groups, but not self-paced. As demonstrated by this meta-analysis, very few studies have assessed acute neural responses and the variability within those studies was high (Mason et al. 2018). Until more studies can be included, it is possible the heterogeneity in acute MEP amplitude responses to resistance training could be explained by methodological inconsistencies.

Paired-pulse protocols have highlighted responses to a single resistance training session in M1 synapses. Intracortical inhibition may be dampened after a single resistance training session, as indicated by a reduction in cSP (Latella et al. 2017). However, SICI measures have been inconclusive. Self-paced training yielded reduced inhibition immediately after training (Leung et al. 2015), while metronome-paced (Leung et al. 2015), hypertrophic, and heavy-strength

training exhibited no change (Latella et al. 2018; Latella et al. 2017). It is possible the variance is due to the comparison of multiple training types. ICF protocols indicate no change in intracortical excitability (Latella et al. 2016; Latella et al. 2017; Latella et al. 2018). Much of the literature on acute responses are also from the same lab, increasing the risk of bias. Similar to single-pulse MEP data, it is difficult to draw conclusions on acute responses to resistance training when meta-analyses include so few studies with an assortment of training types.

4.2 Short-term neural adaptations to resistance training

A number of intervention studies have been conducted with the aim of determining what regions of the central nervous system (CNS) contribute to short-term improvements in force production. Adaptations have been found to occur in M1 (Beck et al. 2007; Kidgell & Pearce 2010) and the CST (Kidgell et al. 2010; Griffin & Cafarelli 2007). Although, multiple resistance training interventions found no changes in the same TMS output responses both cortically (Kidgell et al. 2010) and subcortically (Lee et al. 2009). Meta-analyses have attempted to synthesize these inconsistent findings in the literature, but still, CNS adaptations to resistance training and their relationship to improvements in force production remain unclear.

A meta-analysis by Kidgell et al. (2017) investigated the mechanism behind neural adaptations to short-term resistance training (2-5 weeks) among untrained individuals by analyzing changes in excitatory and inhibitory corticospinal function. Significant increases in strength were observed across all articles (19 studies total), which is an important indicator of the effectiveness of a program. Pooled data analyses found no change in motor threshold (n = 12) and an increase in MEP amplitude (n = 19). A moderate decrease was found in cSP (n = 6) and a large decrease in SICI (n = 6). These findings indicate the primary mechanisms for neural adaptation are reduced intracortical, and possibly corticospinal, inhibition and some augmented CST excitability (Kidgell et al. 2017). It should be highlighted that the meta-analysis is limited by including very few studies in the analysis of most output measures.

A subsequent meta-analysis found similar results with reportedly less bias due to more studies including a control comparison (Siddique et al. 2020). This meta-analysis used the same inclusion/exclusion criteria as Kidgell et al. (2017) and analyzed 30 studies; all but two studies from Kidgell et al. (2017) were included, as well as additional qualified studies. Siddique et al. (2020) also separated training types within the same study for analysis. Increased MEP amplitude

during voluntary contraction indicated augmented corticospinal excitability with a greater effect (standard mean difference [SMD] = 0.55) than Kidgell et al. (2017) (SMD = 0.27). These enhanced adaptations occurred despite more moderate strength improvements (SMD = 0.67) than the previous meta-analysis (SMD = 0.84). It would have been interesting to observe the correlation between strength gains and the different TMS response variables. cSPs were reduced (SMD = 0.65) and consistent with previous findings of decreased corticospinal inhibition (SMD = 0.66). SICI measured during voluntary contraction yielded a moderate reduction in intracortical inhibition (SMD = 0.68) with a smaller effect than Kidgell et al. (2017) (SMD = 1.00). Siddique et al. (2020) concluded that short-term resistance training causes subtle changes throughout the cortico-motoneuronal pathway to both excitatory and inhibitory synapses.

The limited literature has not revealed a predominant CNS site that augments neural drive after resistance training. Researchers have emphasized that CST adaptations and their mechanisms are not fully understood, and more high-quality investigations are needed (Kidgell et al. 2017; Siddique et al. 2020). CNS adaptations have been found after only a few weeks of training. Mason et al. (2020), for example, found augmentation of descending drive after just 2 weeks of resistance training, as demonstrated by increases in CST excitability (trained: 45 ± 39% increase in MEP area, control: 0.2 ± 2.6% increase in MEP area) and reduction in cortical inhibition (trained: 8 ± 3.9% reduction in cSP, control: 1.1 ± 1.3% reduction in cSP). Yet, there is still a need for studies with longer resistance training programs given that 76% of the studies from Siddique et al. (2020) were ≤ 4 weeks.

4.3 Evidence for reticulospinal adaptations to resistance training

The previously discussed literature has attempted to understand the intracortical and corticospinal mechanisms underpinning neural adaptations to resistance training with inconclusive findings. To date, there is no human-based evidence for the RST mediating strength gain (Akalu et al. 2023; Atkinson et al. 2022). The theory of reticulospinal contribution to resistance training currently relies on observations from cross-sectional analyses of motor function in humans. Superior grip strength in healthy humans was associated with augmented RST excitability in older adults (Maitland & Baker 2021). StartReact results have also revealed enhanced RST activation in stroke (Choudhury et al. 2019) and spinal cord injury patients (Baker & Perez 2017), indicating RST adaptation to compensate for CST damage. A randomized controlled trial in the

form of a resistance training intervention would provide better evidence for a causal relationship between resistance training and RST adaptation.

The nonhuman primate work of Glover & Baker (2022) provided important mechanistic insights into contributions of the CST and RST to force production through invasive techniques. Indwelling electrodes were placed in neurons of the pyramidal tract and reticular formation to measure force coding during voluntary contractions. When the macaques pulled a handle (0.5-6 kg), the greatest firing rates occurred at heavier weights for reticular formation neurons, while peak firing rates in pyramidal neurons were distributed across weights. A linear regression model was fit to observe force-firing rate based on peak firing rates and force. The vast majority of reticular formation neurons with a significant correlation exhibited a positive relationship (20/21 cells), and pyramidal tract neurons were evenly split between positive (22 cells) and negative correlations (21 cells). This indicates that reticular neurons coded force more than corticospinal neurons at peak firing rates. Additionally, reticular formation neurons typically produced one larger peak in firing rate across the contraction, while pyramidal tract neurons produced multiple smaller peaks with more heterogeneity. The authors concluded that both tracts are involved in force production; the CST is likely important for fine adjustments and the RST signals for general force generation (Glover & Baker 2022).

At this point, the only study to implement a resistance training intervention with the purpose of investigating the RST is Glover & Baker (2020). Two macaque monkeys performed an 8-to-9-week (5 sessions/week) progressive resistance training program. Each training session consisted of 50 unloaded trials with direct electrical brain stimulation, 50 loaded trials without stimulation, and a repeat of the 50 unloaded trials with stimulation to assess acute adaptations. The stimulations were applied to intercortical, CST, and RST neurons via indwelling electrodes on the M1, pyramidal tract, and medial longitudinal fasciculus, respectively (Figure 7). The monkeys had bilateral indwelling electrodes in the first dorsal interosseous, flexor digitorum superficialis, flexor carpi radialis, extensor digitorum communis, biceps brachii, triceps brachii, pectoralis major, and posterior deltoid muscles for MEP recordings.

Glover & Baker (2020) had complementary cortical findings to human data (Kidgell et al. 2017) where MEP facilitation was observed in M1, not the pyramidal tract, indicating adaptation among intracortical circuits rather than at the spinal or motor neuronal level. Evidence for RST adaptation was observed from medial longitudinal fasciculus MEP facilitation. Additionally,

augmented synaptic efficacy in specific spinal cord regions revealed RST output changed interneuron and motor neuron connections on the trained arm (Figure 7d & g). Glover & Baker (2020) provided an intricate study of the intracortical, corticospinal, and reticulospinal mechanisms behind neural adaptations to resistance training. This pivotal study has reinforced the need for human research of reticulospinal adaptations to resistance training.

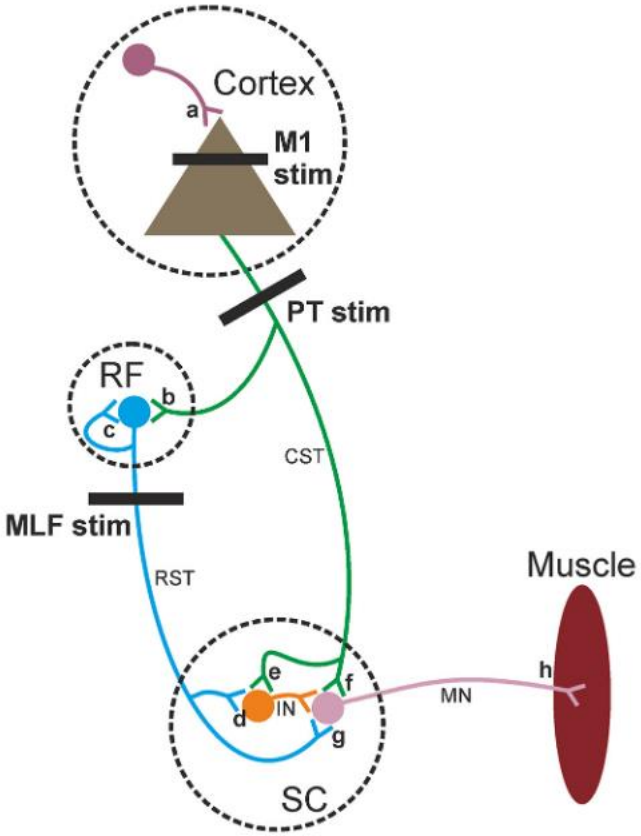

FIGURE 7. Diagram of pathways relevant to findings from Glover & Baker (2020). Stimulation was delivered at the primary motor cortex (M1), pyramidal tract (PT) and medial longitudinal fasciculus (MLF) of the reticular formation (RF). These stimulation points differentiated adaptations to the cortex, corticospinal tract (CST), reticulospinal tract (RST), interneurons (IN) in the spinal cord (SC), and α-motor neurons (MN). Lower-case letters denote synapses relevant to the pathways.

5 PURPOSE OF THE THESIS

Cross-sectional studies of reticulospinal function in clinical populations have provided important insight but are methodologically limited because they cannot demonstrate causality. Animal models have also been an invaluable resource in anatomical and functional investigations of descending pathways but there are differences in the nervous systems of humans and nonhuman primates, especially in the CST (Lemon 2008). It is clear that a resistance training intervention in humans is needed to investigate the corticospinal and reticulospinal contributions to neural adaptations to short-term resistance training. The purpose of this thesis was to address the following:

Research question 1: Does function of the CST and RST adapt to a 6-week resistance training program?
Hypothesis 1: Resistance training will enhance functionality of both the CST and RST by augmenting excitability, reducing inhibition, or both.
Justification 1: Previous studies implementing resistance training interventions have suggested greater CST excitability and reduced cortical inhibition (Siddique et al. 2020). Regarding the RST, human populations with CST damage have presented with increased reticulospinal excitability (Baker & Perez 2017; Choudhury et al. 2019; Akalu et al. 2023), and grip strength has been associated with greater RST excitability in healthy individuals (Maitland & Baker 2021). Finally, nonhuman primate work found both the CST and RST contributed to force production (Glover & Baker 2022), and an 8-to-9-week resistance training program yielded facilitated responses in M1 and motor nuclei of the reticular formation (Glover & Baker 2020).

Research question 2: Are adaptations of the CST and RST dependent on resistance training type (sustained contractions vs explosive contractions)?
Hypothesis 2: Motor pathway adaptations are modulated by training stimuli, thus the training types will yield different CST and RST adaptations.
Justification 2: Both maximal and explosive strength are beneficial in maintaining and improving mobility (Hunter et al. 2004). Differing neuronal firing patterns between the CST and RST during voluntary force production (Glover & Baker 2022) and varied neural responses between training types (Mason et al. 2018; Balshaw et al. 2016) support this hypothesis.

The study consisted of two training groups performing contractions which targeted maximal (sustained contractions) and explosive strength (explosive contractions), as well as a control group given no training program. The study was a semi-randomized controlled trial where healthy young men completed the at-home resistance training program using a custom device, which allowed for isometric elbow flexion. A series of non-invasive neurophysiological measures, including TMS paradigms, were used pre- and post-training to assess adaptations of motor pathways innervating the biceps brachii muscle.

6 METHODS

6.1 Participants

A voluntary response sample of 14 healthy young males (27.5 ± 5.7 years) participated in the study. One participant did not complete the final experimental session, leaving a final sample of 13. Inclusion criteria were right handedness (by verbal confirmation), untrained (no consistent upper-body training within 12 months), and aged 18-35. Participants were to be excluded if they reported any contraindications to TMS (Rossi et al. 2021) or conditions that impacted neuromuscular function of the upper limbs. Participants provided written informed consent, which was approved by the ethics committee of the Faculty of Medical Sciences at Newcastle University (ethical approval references: 23483/2022 and 2344/23580). The study was conducted in accordance with the Declaration of Helsinki.

6.2 Experimental design

The study consisted of three laboratory sessions, one familiarization and two experimental. Height, weight, body composition by bioimpedance analysis (TANITA BC-545N, Amsterdam, Netherlands), MVCs, and relevant medical history were acquired in the familiarization session. Additionally, participants practiced the explosive contractions, and were exposed to the octet stimulation to ensure they could tolerate the electrical stimulation.

If cleared to continue, participants returned for the first experimental session about 1 week later (7.4 ± 4.8 days). Participants were semi-randomly divided into three training groups: control (n = 5), explosive contractions (n = 4), and sustained contractions (n = 4). The first 9 participants were randomly assigned and the following 4 were allocated by matching MVC. The 6-week resistance training program targeting the elbow flexors was initiated within 3 days of the first experimental session, and participants were intended to return for their final laboratory visit 2-4 days after their final training session (4.4 ± 2.2 days, n = 8). The same protocol was conducted for the two experimental sessions, with body composition measures repeated in the final session. Figure 8 provides a graphic of the timeline for each experimental session.

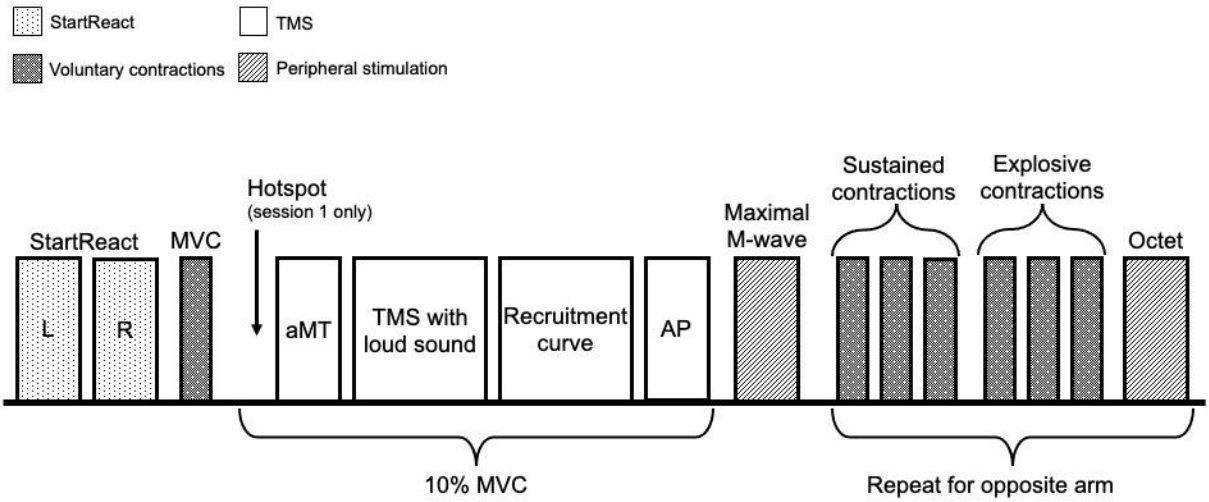

FIGURE 8. Order of assessments in the two experimental sessions. *L*, left arm; *R*, right arm; *MVC*, maximal voluntary contraction; *aMT*, active motor threshold; *AP*, anterior-posterior; *TMS*, transcranial magnetic stimulation.

6.3 Resistance training program

Those allocated to resistance training groups conducted a 6-week at-home intervention. Training was prescribed three times per week, for 18 sessions in total, with each session separated by at least 1 day. Participants were instructed to perform each session at a similar time of day. The training program utilized a custom device containing a load cell which captured force production from isometric contractions at the elbow joint on both arms (Figure 9). Isometric contractions were used for this study to avoid changes in elbow joint angle. The device held the elbow joint at 90° and participants were instructed to maintain a neutral shoulder position with their forearm supinated. Padding was added to customize the device to the participant's arm and forearm size. Participants were provided with instruction for the training in the first experimental visit.

FIGURE 9. Custom at-home isometric resistance training device

The custom device allowed for visual feedback to the participant via wireless connection to a website with the individualized training program. Participants could access the website on a mobile phone or desktop. Each participant was given an account that guided them through the appropriate contractions for the given training session and group (Figure 10a). This remote instruction was intended to ensure consistency in magnitude of contractions, as well as timing of repetitions. The web app had the capacity for progressive training by collecting MVC data every third session (1x/week). A set of three maximal contractions (3-s duration) were performed and training intensities were adapted to the individual's changes in strength. Completed sessions were made immediately accessible to the researcher so training adherence could be followed in real-time.

Each training session included a device calibration, warm-up, and 4 sets of 10 repetitions with a 5-s rest between repetitions. Two minutes of rest was given between sets. All sets on the right arm were completed before training the left arm. If the session called for MVCs, they occurred after the warm-up with a 60-s rest between the three repetitions. Participants could view their force trace in real-time with a reference line of their previous best MVC.

Both explosive and sustained training programs were replicated from Balshaw et al. (2016). The explosive group was provided with a target line at 80% MVC and were instructed to perform a contraction "as hard and as fast as possible." They were to produce a contraction, which reached at least 80% MVC (Figure 10b). A scale was also displayed above the force trace, which reported rate of force development (RFD). Participants were not given a goal torque value, rather the scale

provided feedback on the previous contraction. The sustained group followed their target line, which progressed from zero and plateaued at 75% MVC (Figure 10c). They performed a 1-s build to 75% MVC and held that intensity for an additional 2 s, followed by a 5-s rest between repetitions.

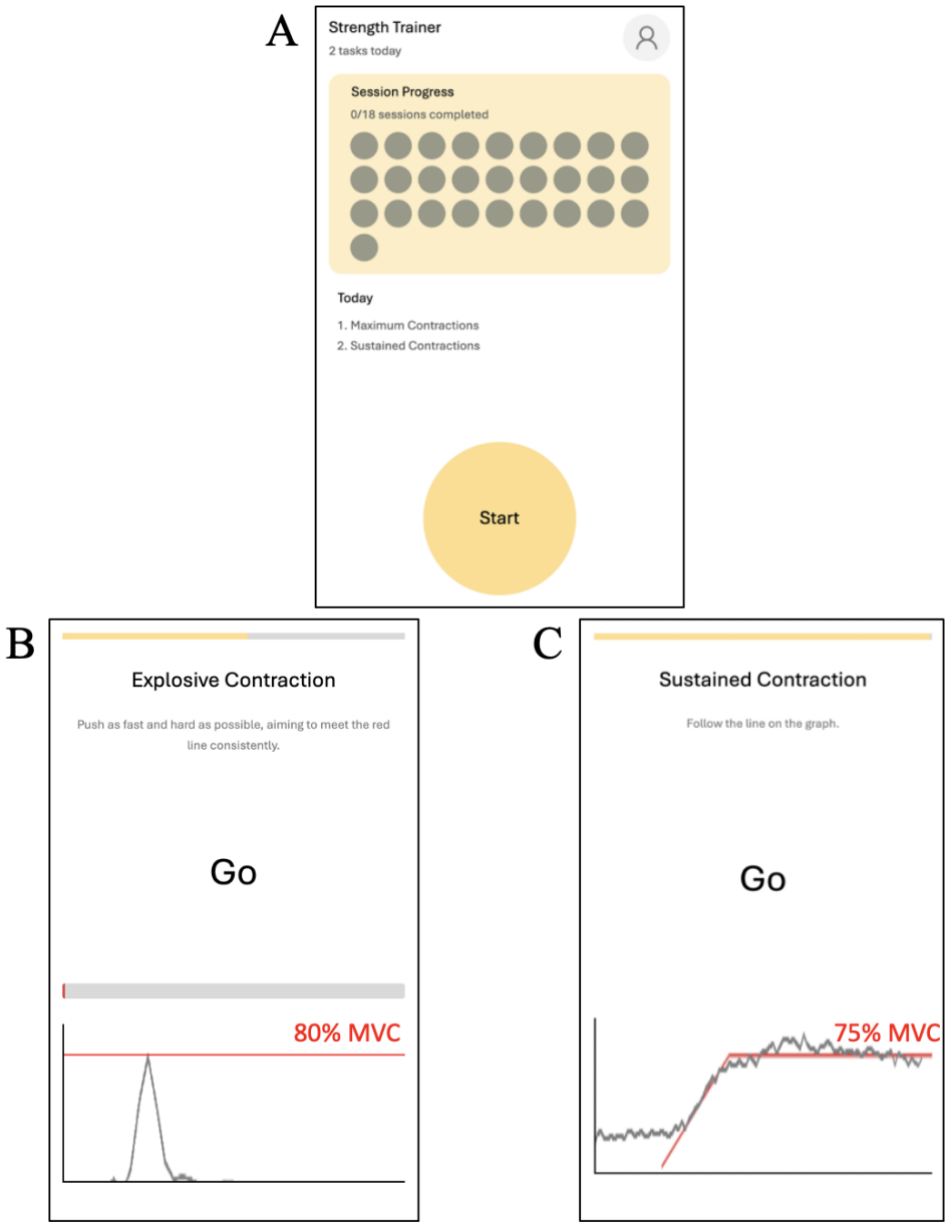

FIGURE 10. Online resistance training program. The home screen (A) displayed the day's training plan and a record of completed sessions. The grey circles turned green when a session was completed and saved. Explosive (B) and sustained (C) training programs displayed real-time force production in grey. *MVC*, maximal voluntary contraction.

6.4 Electromyography and force recording

EMG data was collected from the biceps and brachioradialis muscles with bipolar Ag/AgCl electrodes (50 mm^2 sensor area, Kendall H93SG, Cardinal Health, UK). One electrode was placed over the mid-point of the respective muscle and a second was placed 2 cm distally. The reference electrode was placed on the medial aspect of the arm. Locations were recorded with photographs to improve consistency in placement between the experimental sessions.

EMG and force data were recorded at a sampling rate of 5 kHz and 1 kHz, respectively, using Spike2 computer software (Cambridge Electronic Design Ltd., UK). EMG was amplified at a gain of 500 and a high-pass filter of 30 Hz was applied (D360 Amplifier, input impedance >100 MΩ, Digitimer Ltd., UK). A MATLAB program applied an acausal Gaussian filter (± 250 ms, 10 ms standard deviation [SD]) to force signals.

6.5 Force production assessments

Participants placed their arm in a device containing a load cell to measure force produced from isometric elbow flexion. The apparatus held the shoulder and elbow at about 90° and the forearm was supinated. EMG data was collected from the brachioradialis and biceps brachii on the right arm. A computer monitor was placed on a table 0.5 m in front of the participant for continuous force production feedback.

6.5.1 Maximal and explosive strength

A series of sustained contractions were conducted to determine the participant's MVC, and explosive contractions to assess maximal RFD. A set of three attempts were given for each contraction type with a 60-s rest between trials. First, participants were instructed to contract "as hard as possible" for the sustained contractions. An audible cue was given from the Spike2 system to begin and stop their 3-s sustained contractions. Participants were given motivation through a trace of their force production and a reference to their best previous attempt, as well as verbal encouragement from researchers. The greatest force production value achieved across the three trials was recorded for each arm as the MVC for the session.

Explosive contractions were conducted in a similar manner, but participants were instructed to contract "as hard and as fast as possible" when they heard the same 'go' cue. A line at 80% MVC was displayed on the force trace and participants were asked to contract to at least 80% MVC. It was especially important that participants were familiarized with the explosive contractions in their familiarization visit as many had trouble producing the ballistic movement. RFD was defined as the change in force from contraction onset to 50 ms post contraction onset. Contraction onset was determined using MATLAB (once 1.5% MVC was reached) and the greatest 0-50 ms slope across the three attempts for each arm was recorded as maximal RFD.

6.5.2 Maximum electrically-evoked twitch

A maximum electrically-evoked twitch was collected to assess maximal force output by the biceps brachii, independent of neural activation by the musculocutaneous nerve. The experimental protocol was based on Balshaw et al. (2016). A stimulator DS7AH digitimer (Digitimer Ltd, UK) delivered square pulses (300 Hz, 200 μs duration, 5 s apart) through custom-made rectangular steel plates (1 cm x 2.5 cm) wrapped in saline-soaked cloth. The cathode electrode was taped to the mid-point of the biceps muscle belly and the anode was placed 2 cm distally. Force produced by the twitch response was observed as current intensity was increased manually from 50 mA until the peak twitch response plateaued. The final intensity was used for the supramaximal octet stimulations.

The octet is a series of 8 pulse trains (300 Hz, 200 μs duration) that evokes maximal contractions. Three octets were delivered with a 20-s rest period. The rest period was randomized by ± 3 s to prevent anticipation by the participant. Peak force reached within the first 80 ms from contraction onset was recorded for analysis. The maximum electrically-evoked twitch was the highest peak force across the 3 trials for each arm.

6.6 StartReact test

The StartReact test is a well-established non-invasive measure of reticulospinal function (Tapia et al. 2022). A previously tested protocol (Baker & Perez 2017) was implemented in this study. Participants reacted as quickly as possible to a red LED light flash by flexing their elbow. EMG data were collected throughout from the brachioradialis and biceps brachii muscles with bipolar surface electrodes. Three stimulus conditions were given: 1) LED light alone; 2) LED light with

a quiet sound (80 dB, 1000 Hz, 50 ms); 3) LED light with a loud sound (120 dB). Sounds were delivered through two audio speakers (JBL, Control One, USA; Eltax Acura Amp-70 Integrated Amplifier, France) on a table 0.5 m in front of the participant. Twenty trials per condition were delivered with an ISI of 8 s. Stimuli were delivered in a pseudorandomized order with the first six stimuli a sequence of two LED only, two LED with quiet sound, and two LED with loud sound. Participants were seated with their hand rested on a table and instructed to flex around their elbow as quickly as possible when they saw the LED light flash. A few familiarization trials were conducted before measures on each arm. The protocol was first conducted on the left arm, then repeated on the right.

Data were analyzed semi-automatically using a custom MATLAB script (R2020b, MathWorks). The script applied a 500 Hz low-pass filter to the unrectified EMG signal. Reaction time was identified as the time from stimulus to onset of rectified EMG activity that exceeded 7 SDs above the mean 200 ms before stimulus. Reaction time to the light alone was defined as the visual reaction time (VRT), and visual-auditory reaction time (VART) when accompanied by the quiet sound. Reaction time to the light and loud stimulus was defined as the visual + startle reaction time (VSRT). Each trial was examined visually, while blinded to the trial condition, to confirm the automatic placement. The difference between average VSRT and VART (StartReact effect) was calculated to determine RST function. A greater StartReact effect indicates enhanced RST excitability (Valls-Solé et al. 1999).

6.7 Transcranial magnetic stimulation assessments

A figure-of-eight coil (70cm diameter, D70 Alpha Flat Coated coil) and Magstim BiStim^2 magnetic stimulator (Magstim, UK) were used to deliver monophasic current waveforms. The TMS measures all targeted activity of the right biceps brachii with all stimuli delivered to the contralateral motor cortex. The Brainsight TMS Navigation system (Brainbox, Rogue Research Inc., Canada) paired with a Polaris Spectra camera (Northern Digital Inc., Canada) were used to improve precision of coil placement across the study. The participant wore a headband with three motion capture markers over the forehead so the system could track their head position. The Brainsight system calls for digital marking of the nasion and tragus of each ear during set-up to establish baseline reference points of the motion capture markers relative to the head. A pen was used to mark the location of these three points and photographs were used to improve registration accuracy in the post-intervention assessment.

The coil was held at a 45° angle to the parasagittal plane to induce a current in the left motor cortex in a PA current direction. The coil was also fitted with three motion capture markers for its location to be distinguished by the navigation system. The optimal stimulation location which produced the largest MEP responses from the biceps (hotspot) was recorded with the navigation system so stimuli remained as consistent as possible across assessments and laboratory visits.

Participants placed their arm in the same device as previously mentioned (section 6.5) to measure force produced from isometric elbow flexion throughout TMS protocols. The computer monitor provided continuous EMG feedback in the form of a color gradient for the participant to maintain 10% MVC during all TMS assessments. The aMT was determined as the lowest TMS intensity which yielded a MEP amplitude of > 100 μV in 5/10 trials with the participant contracting at 10% MVC.

6.7.1 Recruitment curve

The recruitment curve is an assessment of CST function with its output measures (i.e., slope, horizontal asymptote, and stimulator output at half maximum) reflecting CST excitability. TMS was delivered to the hotspot in the PA current direction as the participant contracted at 10% MVC. The recruitment curve began with the aMT stimulator output intensity and was increased by intervals of 10% maximum stimulator output. Ten stimulations were delivered per intensity with an ISI of 5 s. MEP characteristics were analyzed by a MATLAB program. Regions of the average rectified MEP were manually marked. Onset of the MEP was marked when EMG voltage surpassed ± 2 SD and the end was marked at return to baseline (determined by mean EMG activity 200 ms prior to stimulation).

6.7.2 Loud acoustic stimulation with TMS

The pairing of LAS with TMS protocol relies on a similar principle as the StartReact test where targeting of subcortical structures with a loud sound allows for RST assessment (Germann & Baker 2021). With the participant contracting at 10% MVC, TMS pulses were delivered in the PA current direction at at intensity of 120% aMT. The TMS stimulus was delivered alone or proceeded by a loud sound (120 dB, 500 Hz, 50 ms duration) using the same speaker system as the StartReact test. The loud sound was 50 ms before the TMS pulse. The 50 ms ISI and 120 dB

sound were chosen based on findings that an ISI of 30-60 ms and $\geq$ 80 dB produces significant MEP suppression (Furubayashi et al. 2000). The protocol consisted of 20 stimuli, 10 for each condition, presented in a randomized order.

The same previously mentioned analysis method for identifying MEP regions was utilized for the average control MEP (TMS only condition). The same regions were then used for the conditioned MEP (LAS + TMS condition), and integrals of the average MEP for each condition were analyzed. Ultimately, the integral of the average conditioned MEP was calculated as a percentage of the average control MEP to report MEP suppression. The extent of MEP suppression has been shown to reflect RST function (Furubayashi et al. 2000). Integral, duration, latency, and cSP of the average rectified MEP from the control condition were also analyzed for comparison to the AP current orientation MEPs. An acausal Gaussian filter (± 450 ms, 5 ms SD) was included in the MATLAB program only for cSP analyses. The filter was applied to cSP analysis to accurately identify the return of the EMG signal to baseline.

6.7.3 Anterior-posterior current direction assessment

The coil was rotated 180° to the AP current direction while maintaining the hotspot and tilt angle relative to the scalp. The aMT procedure was repeated in the new orientation and a set of 20 stimulations were delivered at 120% aMT with the participant contracting at 10% MVC. The ISI remained the same, at 5 s. The same previously mentioned analysis method for identifying MEP regions was utilized. Integral, latency, and duration of the average rectified MEP were analyzed using MATLAB for comparison to PA MEPs from the LAS + TMS protocol's control MEPs.

6.8 Maximal compound action potential

The maximal compound action potential (M_{max}) was collected from electrical stimulation (300 Hz, 200 μs, square pulses) of the musculocutaneous nerve. Stimulation electrodes (Kendall H34SG, Cardinal Health, UK) were placed on the right shoulder with the cathode electrode in Erb's point (supraclavicular fossa) and anode on the acromion process. A single familiarization stimulation was given at 20 mA, followed by two 90 mA and two 100 mA stimulations. MEPs from TMS assessments were normalized as a percentage of the M_{max}, allowing comparison between repeated visits irrespective of changes in electrode placement on the biceps.

6.9 Statistical analyses

The assumptions for parametric testing were not met due to the small group sample sizes ($n \leq 5$). Therefore, initial statistical analyses were conducted using non-parametric tests. Kruskal-Wallis tests were performed to examine differences in group characteristics at baseline, and Wilcoxon signed rank tests were performed for pre- and post-intervention comparisons. However, Wilcoxon tests on samples where $n < 5$ will not yield a *p*-value < 0.05 (Howell 2010). All reported statistical analyses are drawn from subsequent parametric tests when data were normally distributed. Between-group comparisons were calculated for baseline group characteristics with one-way ANOVAs. Within-group comparisons were performed with paired-sample t-tests. Statistical analyses between intervention groups, apart from baseline characteristics, were not performed due to small sample sizes.

Results are reported as mean ± SD. The alpha level of 0.05 was adjusted to 0.016 ($\alpha = 0.05/3$) to correct for variables with 3 comparisons. Hedges' g was used to calculate effect sizes with the following cutoffs for interpretation: small effect = 0.2, medium effect = 0.5, large effect = 0.8 (Hedges & Olkin 1985). All statistical analyses were conducted on SPSS Statistics Version 28.0 (IBM, Armonk, NY).

7 RESULTS

7.1 Baseline characteristics

Baseline MVC (control: 187 ± 79 N, explosive: 193 ± 26 N, sustained: 249 ± 75 N, $p = 0.359$) and octet (control: 52 ± 7 N, explosive: 41 ± 13 N, sustained: 55 ± 13, $p = 0.262$) of the right arm did not differ between intervention groups. Similarly, a significant difference was not found in MVC ($p = 0.313$) and octet ($p = 0.771$) of the left arm. There were also no differences in age between groups (control: 26.2 ± 5.8 years, explosive: 29.3 ± 7.7 years, sustained: 27.3 ± 4.3 years, $p = 0.757$).

7.2 Strength assessments and octet

Significant improvements in MVC were not observed across groups in either arm ($p = 0.072$-0.696; Figure 11a). Although, a trend of increased MVC was observed in the explosive group for the right arm (193 ± 26 N vs. 224 ± 19 N, $p = 0.072$, Hedges $g = 1.184$). The explosive training group also exhibited a trend of increased RFD on the right arm with improvements in all participants (1693 ± 536 N/s vs. 2598 ± 881 N/s, $p = 0.039$, Hedges $g = 1.523$; Figure 11b), but these changes were not significant with respect to the adjusted α-level. Significant changes in RFD were not found in the control ($p = 0.170$) or sustained groups ($p = 0.997$) for the right arm, or any group for the left arm (control: $p = 0.476$, explosive: $p = 0.385$, sustained: $p = 1.000$). Significant changes in octet response were not observed in any group on either arm ($p = 0.208$-0.985; Figure 11c). Three participants (control: n = 2, sustained: n = 1) were excluded from analysis of the right octet because octets were too small and not physiologically valid.

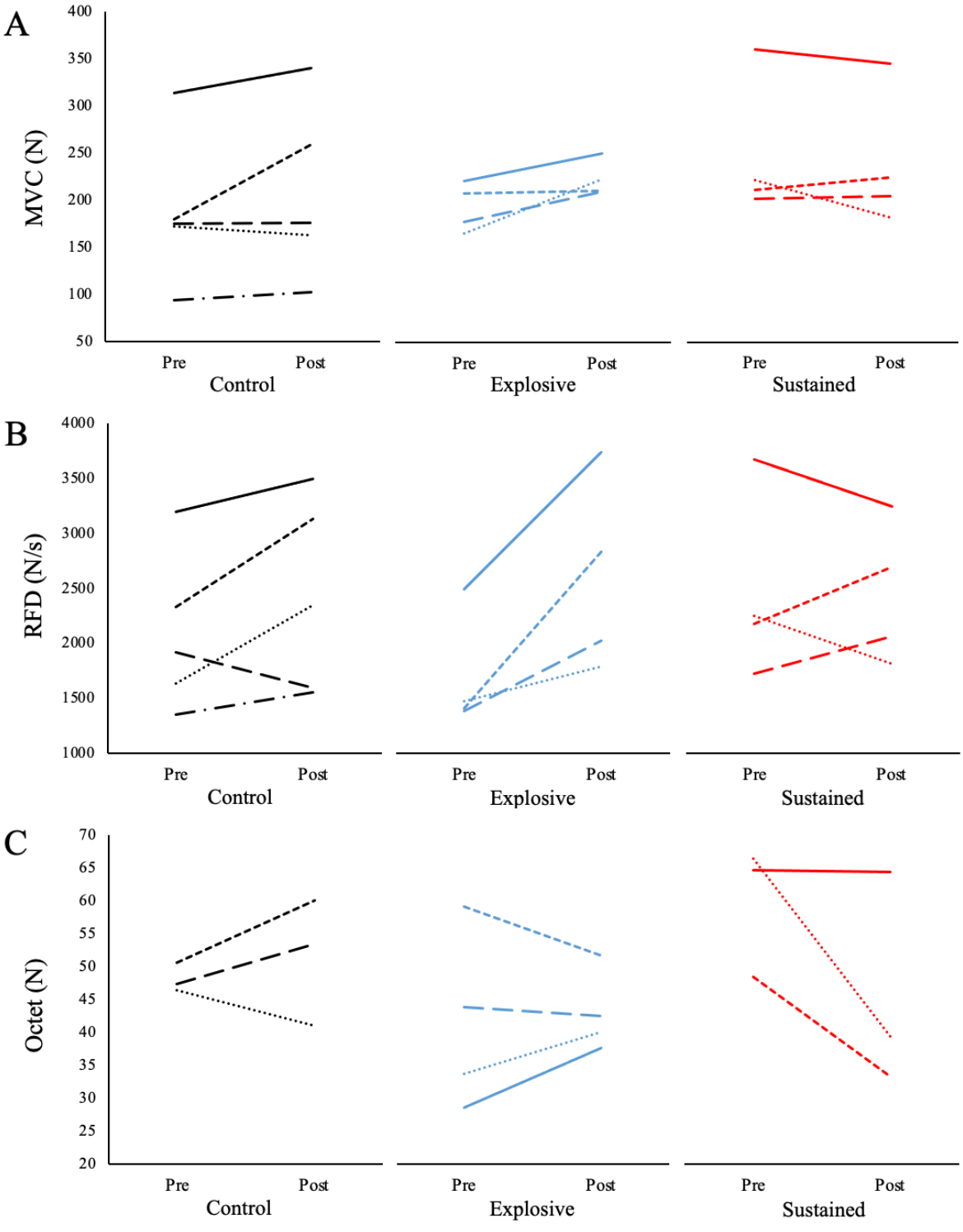

FIGURE 11. (**A**) Maximal voluntary contraction (MVC), (**B**) rate of force development (RFD), and (**C**) octet responses for the right arm of each participant pre- and post-intervention. Line patterns are consistent across variables for each participant and with Figures 13-15.

7.3 StartReact test

A significant StartReact effect was observed in both arms pre- and post-intervention (Figure 12). This effect was demonstrated with significantly shorter VSRTs than VARTs (p = 0.001 for all comparisons). These within-session analyses of the StartReact test were calculated with non-parametric tests (Wilcoxon) as data for the right arm were not normally distributed.

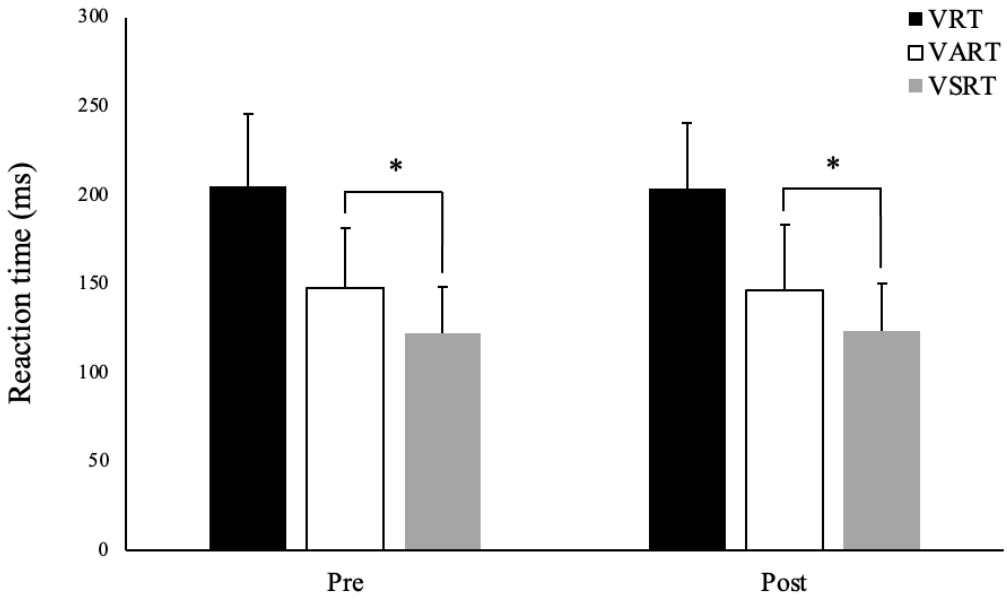

FIGURE 12. StartReact test reaction times for the right arm across all groups (n = 13). The reduction in reaction times between visual-auditory reaction time (VART) and visual + startle reaction time (VSRT) demonstrate the StartReact effect. Visual reaction time (VRT) is the light-only condition. Data are presented as means with standard deviation (SD) error bars. * $p < 0.05$, within-group comparison.

StartReact effect values did not exhibit significant changes pre- and post-intervention across groups for the right arm (control: 30.3 ± 27.7 ms vs. 31.9 ± 31.0 ms, p = 0.830; explosive: 16.5 ± 16.5 ms vs. 18.7 ± 14.3 ms, p = 0.146; sustained: 28.1 ± 13.8 ms vs. 16.7 ± 9.5 ms, p = 0.075, Hedges g = 1.167; Figure 13). Only the sustained group reported a trend of decreasing StartReact effect in the right arm. Significant changes were not found in the left arm (control: 29.7 ± 25.3 ms vs. 42.6 ± 25.2 ms, p = 0.199; explosive: 24.4 ± 12.7 ms vs. 10.6 ± 6.6 ms, p = 0.191; sustained: 19.7 ± 5.5 ms vs. 20.9 ± 4.5 ms, p = 0.806).

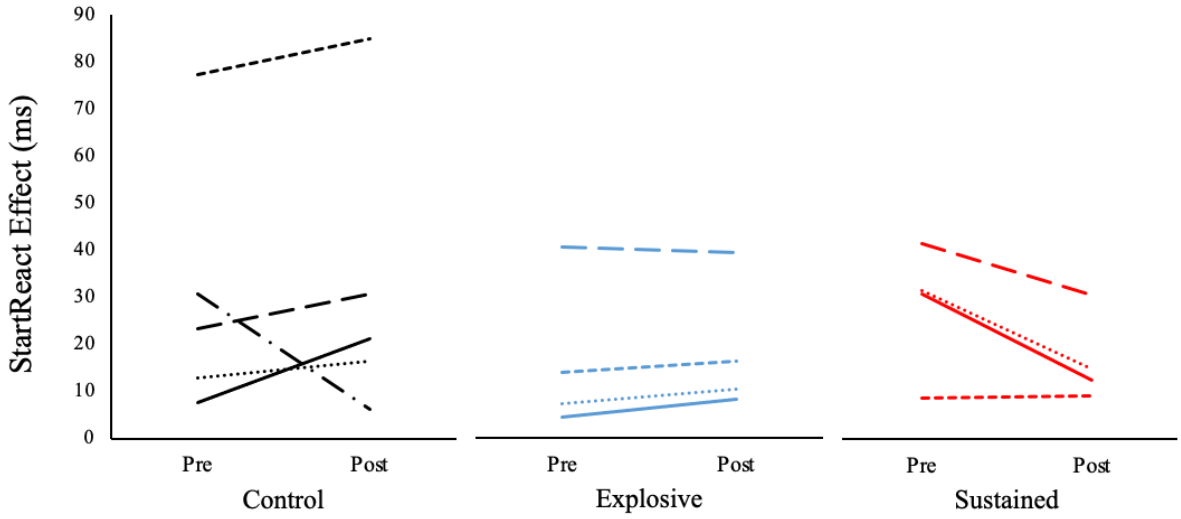

FIGURE 13. StartReact effect pre- and post-intervention for the right arm. StartReact effect is reported as the difference between visual-auditory reaction time (VART) and visual + startle reaction time (VSRT). Note that a larger StartReact effect indicates a greater decline in reaction time from VART to VSRT. Line patterns are consistent with Figures 11, 14 & 15 for each participant.

7.4 Transcranial magnetic stimulation assessments

No significant changes in normalized MEP size were observed for any group in the PA or AP currents (Figure 14). All participants in the explosive group exhibited greater normalized MEP amplitude values for PA current (6.3 ± 2.4% vs. 15.1 ± 13.7%, $p = 0.295$, Hedges $g = 0.595$) and AP current (5.1 ± 2.3% vs. 21.0 ± 19.2%, $p = 0.229$, Hedges $g = 0.720$), but these tendencies across did not yield statistically significant changes. Consistencies were not observed among participants in the control group for normalized PA (5.4 ± 3.9% vs. 7.3 ± 9.0%, $p = 0.695$) or AP MEPs (7.5 ± 7.3% vs. 14.4 ± 17.9%, $p = 0.742$). The sustained group did not have enough valid data for statistical analyses due to errors in M_{max} measurements.

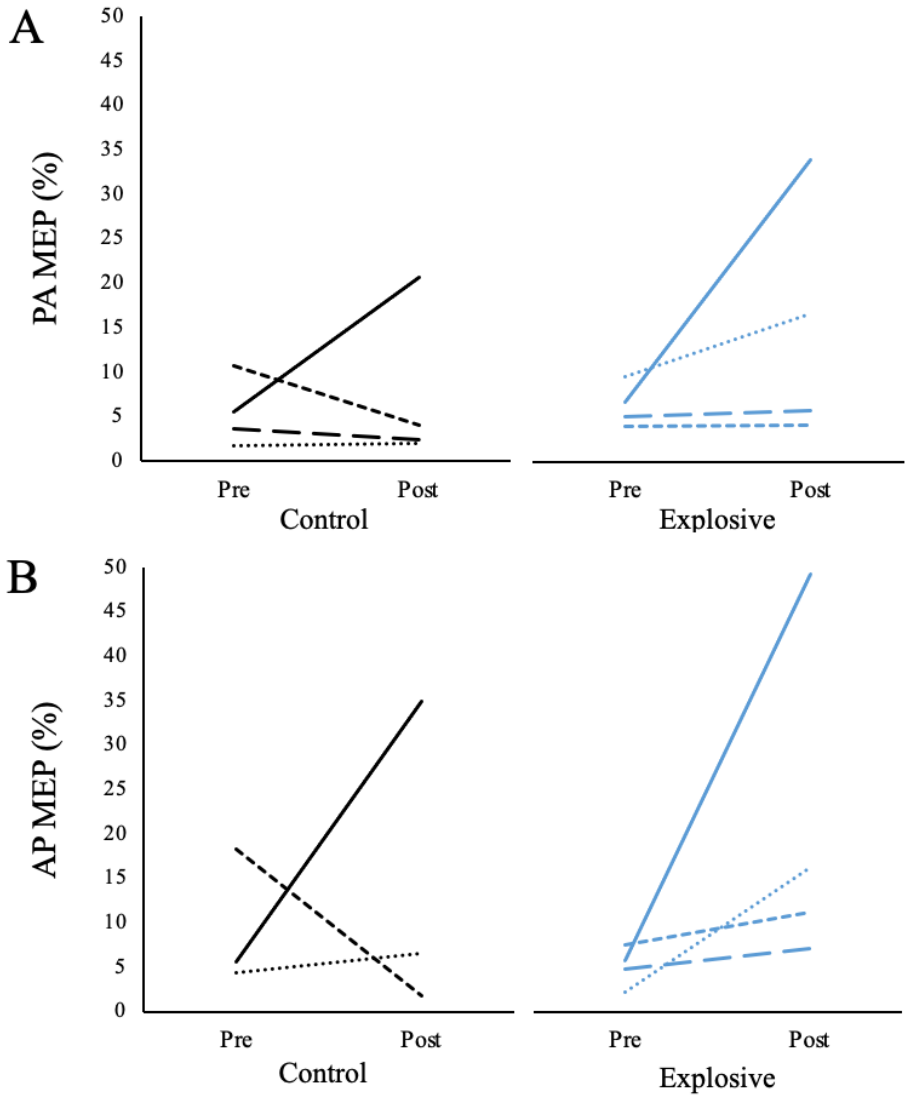

FIGURE 14. Within-group comparisons of normalized motor evoked potentials (MEP) for the (**A**) posterior-anterior (PA) and (**B**) anterior-posterior (AP) current directions. Line patterns are consistent across variables for each participant and with Figures 11, 13 & 15.

No significant changes were found in MEP characteristics (Table 1). A trend toward decreased PA MEP latency (p = 0.030, Hedges g = 0.792) and increased AP MEP duration (p = 0.026, Hedges g = 2.102) were found in the explosive training group. Greater PA aMT values were observed for all participants after explosive training, but these changes were not significant (p = 0.080, Hedges g = 1.091). Within-group trends were not found in the control or sustained groups.

TABLE 1: MEP characteristics pre- and post-intervention

		Control				Explosive				Sustained			
		n	Pre	Post	*p*	n	Pre	Post	*p*	n	Pre	Post	*p*
PA	Active motor threshold (%)	4	49.8 ± 11.8	49.0 ± 9.3	0.380	4	47.3 ± 16.0	54.8 ± 16.1	0.080	4	49.5 ± 6.6	50.0 ± 10.9	0.885
	Latency (ms)	4	13.1 ± 1.5	13.0 ± 0.3	0.914	4	12.4 ± 0.8	12.2 ± 0.8	0.030	4	12.7 ± 0.6	13.1 ± 0.4	0.269
	Duration (ms)	5	22.1 ± 3.1	23.8 ± 5.1	0.428	4	23.5 ± 3.1	25.8 ± 2.6	0.151	4	24.3 ± 3.3	22.9 ± 4.36	0.705
	Silent period (ms)	5	65.8 ± 24.1	83.4 ± 21.3	0.167	4	73.3 ± 20.7	105.3 ± 53.6	0.350	4	65.3 ± 15.5	70.0 ± 26.3	0.804
AP	Active motor threshold (%)	4	72.4 ± 4.2	72.3 ± 12.7	0.829	4	64.5 ± 15.7	75.8 ± 14.0	0.184	4	68.8 ± 10.5	69.3 ± 15.1	0.943
	Latency (ms)	5	14.6 ± 1.6	15.9 ± 3.3	0.539	4	13.2 ± 0.9	12.7 ± 0.6	0.275	4	14.0 ± 1.1	13.3 ± 1.8	0.192
	Duration (ms)	5	23.6 ± 2.1	22.9 ± 4.9	0.430	4	23.5 ± 3.5	28.7 ± 2.5	0.026	4	24.1 ± 2.5	26.4 ± 2.8	0.253
	Coil orientation latency difference (ms)	4	1.4 ± 1.2	1.7 ± 2.4	0.813	4	0.8 ± 1.1	0.6 ± 0.4	0.691	4	1.3 ± 0.6	0.2 ± 1.5	0.097

Suppression of the conditioned MEP in the LAS + TMS measure was observed in the majority of participants pre- (66.7%) and post-intervention (72.7%; Figure 15). A significant change in MEP suppression was not observed in any of the groups (control: 60.1 ± 30.0% vs. 48.5 ± 33.1%, $p = 0.271$; explosive: 90.8 ± 57.4% vs. 71.1 ± 40.5%, $p = 0.373$; sustained: 97.2 ± 51.8% vs. 97.6 ± 23.3%, $p = 0.981$). Data from the control (n = 1) and explosive (n = 1) groups were excluded from analysis due invalid MEPs and an outlier (+ 5.3 SDs pre-intervention), respectively.

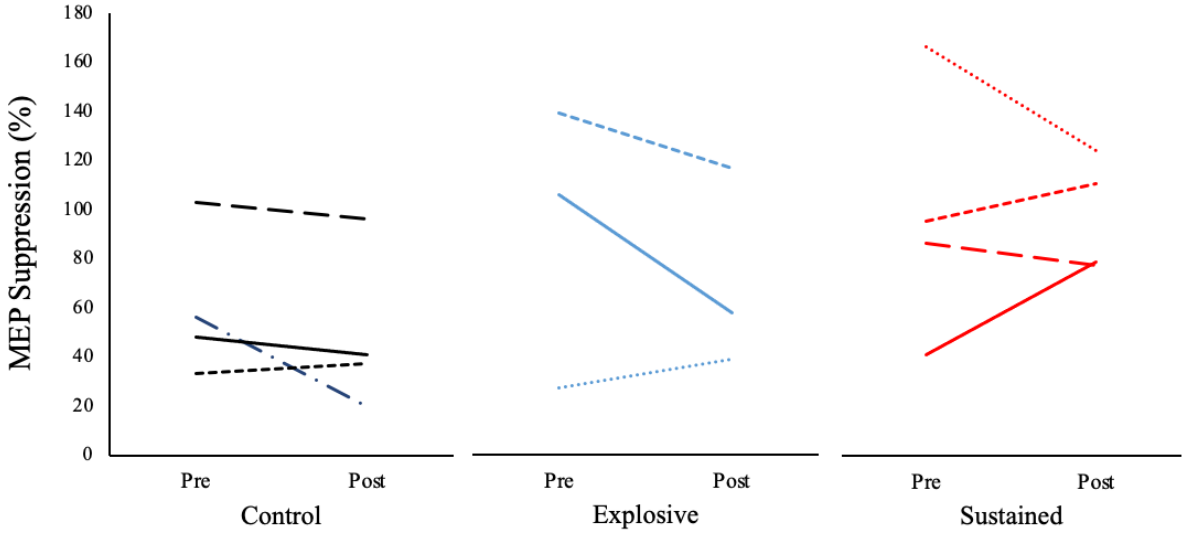

FIGURE 15. Motor evoked potential (MEP) suppression from the LAS + TMS measure pre- and post-intervention. Suppression of the conditioned MEP (LAS + TMS) is presented as a percentage of the control condition (TMS alone). Line patterns are consistent with Figures 11, 13 & 14 for each participant.

8 DISCUSSION

The present thesis investigated corticospinal and reticulospinal adaptation to a short-term resistance training program. Significant strength gains were not observed among maximal or explosive strength-trained participants after the 6-week intervention. Additionally, negligible changes were observed in corticospinal and reticulospinal function for both training types. The preset study was unable to answer research question 1 – whether corticospinal or reticulospinal excitability changes after short-term resistance training. Subsequently, the lack of observed CST or RST adaptation also limited the present study from addressing research question 2 concerning the differences in adaptation of the two tracts between sustained- and explosive-contraction training programs.

8.1 Strength assessments and muscular function

Maximal and explosive strength were quantified by MVC and RFD, respectively. No significant changes in MVC or RFD were found in either arm of the sustained or explosive training groups based on the adjusted alpha level. Measures of maximal and explosive strength are an indication of the efficacy of the resistance training programs. The lack of significant improvements in MVC and RFD in all training groups indicate that the training programs were not effective. Previous studies have demonstrated that a 6-week resistance training program can cause significant maximal and explosive strength gains in untrained populations (Folland & Williams 2007). Limitations in the novel at-home training device (discussed further in section 8.3.1) likely weakened the training program, especially for the sustained-contraction group.

However, it is possible that a small sample size limited the statistical power of the explosive training group, masking group-level strength improvements. Trends toward increasing MVC and RFD with large effect sizes were observed in the explosive training group on the right arm only. Improvements of 16% and 53% for MVC and RFD, respectively, are aligned with previously observed changes in force production after explosive resistance training. Balshaw et al. (2016) reported a 17% increase in maximum voluntary torque and 33% increase in explosive torque over the first 50ms of the contraction after a 12-week intervention. Although, these adaptations were observed in the knee extensors. Hubal et al. (2005) conducted a multicenter study where 243 men completed 12-week resistance training programs and found an average 15.8 ± 1.1% improvement in isometric elbow flexion MVC. Based on comparable relative

improvements in strength compared to other studies with larger sample sizes, and large effect sizes, the trends of increased MVC and RFD in this study may have been statistically significant with a larger sample. Without stronger statistical evidence, it can still only be speculated that maximal and explosive strength were improved by explosive resistance training in the present study.

The presence of non-responders – individuals who do not improve strength in response to a resistance training program – would also have a large impact on these small samples. While the average untrained male may exhibit strength gain (15.8 ± 1.1% increase in MVC) after a 12-week dynamic elbow flexion training, changes have shown to vary from a 32% reduction to 149% increase in MVC (Hubal et al. 2005). Depending on the criteria, low and non-responders have been reported at rates of 17.4% (improved MVC by < 5%, Hubal et al. 2005), 15% (≤ 1 SD, Erskine et al. 2010), and 6.7% (upper 95% CI: 5.0%, Ahtiainen et al. 2016). The present study is especially vulnerable to non-responders because a single low or non-responder in a sample of 4-5 participants would heavily bias group averages. The absence of group-level improvements in strength could be attributed to population-wide heterogeneity in responses to resistance training.

Results from the octet stimulation indicate an absence of muscular adaptation. These findings are consistent with the literature, which attributes early strength gains from a resistance training program to neural adaptations (Moritani & deVries 1979; Balshaw et al. 2016). Hypertrophy is considered a driving muscular adaptation in performance improvements (Folland & Williams 2007). High-load resistance training is generally thought to take 8-12 weeks of training to yield significant increases in anatomical cross-sectional area (Narici et al. 1996). This notion more directly applies to the sustained training group in the present study, while explosive training has shown to induce less hypertrophy. After their 12-week isometric resistance training program, Balshaw et al. (2016) only found hypertrophic effects (+8% in quadriceps volume by MRI) in the sustained-contraction group, not the explosive-contraction training group. Upper-body resistance training, however, has greater hypertrophic effects than lower-body training (Abe et al. 2000), possibly causing earlier hypertrophy in the biceps brachii. In the present study, octet stimulations provide insight into the functional effects of potential muscular adaptations. Octet data did not change after either training intervention, indicating that 6 weeks of resistance training did not induce muscular adaptations (i.e., hypertrophy) that contribute to force production.

Heterogeneity of the data and reduced sample sizes from invalid data (3 participants excluded) should be considered when addressing the validity of the octet test. Participants were excluded because EMG responses were too small, compared to the pre-training session, to be physiologically feasible (Figure 16). Small sample sizes reduced statistical power and the validity of the test could be questioned based on multiple occurrences of invalid octets.

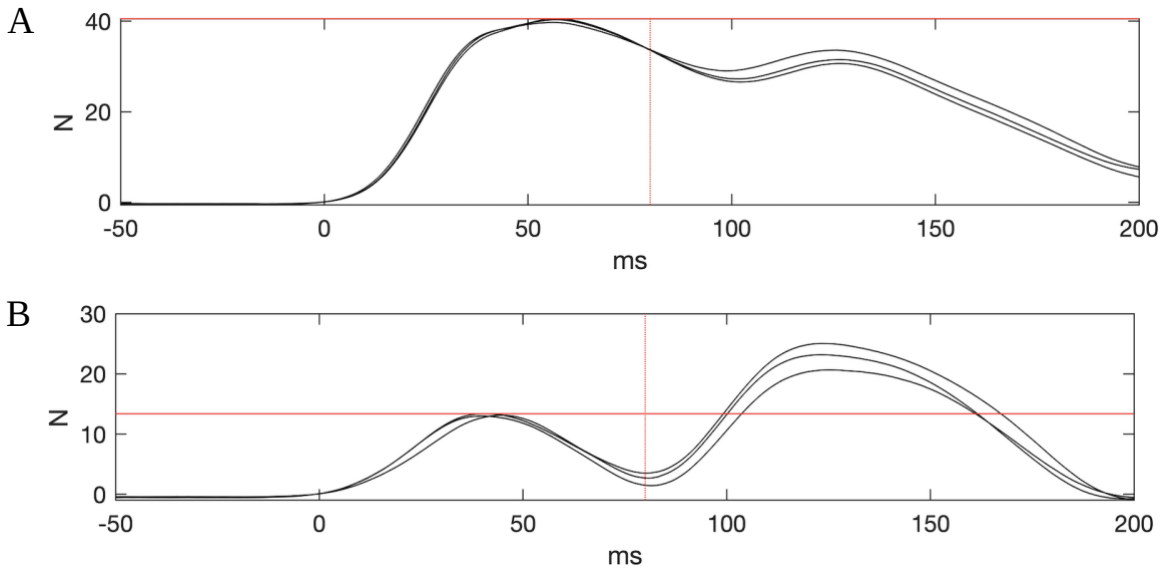

FIGURE 16. Example of an invalid octet waveform. Both octets are from the right arm of the same participant before (A) and after training (B). Each figure consists of force traces of the three trials. The vertical red lines mark the 80 ms cutoff for detecting peak force production. The horizontal red lines mark the reported peak force production. The post-training octet (B) was invalid, thus, the participant was removed from final analysis.

The majority of participants had double-peaked octets with varying degrees of suppression in-between (Figure 16a & b). Invalid octets exhibited a small peak in force production followed by a larger peak (Figure 16b). Regions for detecting peak force production were limited to the first 80 ms after force production onset to ensure only the desired electrically-evoked force response was analyzed. As a result, only the first peak in force production was included in analysis, but was not always the highest peak. These inconsistencies in waveforms could account for the high variability of the octet data. Force signals could have been confounded by reflexes or voluntary contractions observed as early as 30 ms after stimulus onset in hand muscles (Balestra et al. 1992). Although, it could be argued that smaller EMG responses from these early reflexes have negligible contributions to force production. Delayed motor outputs

from later reflexes (~ 75 ms post-stimulus onset) and voluntary contractions could have contributed to later force production, but do not explain the suppression between peaks (Balestra et al. 1992). Based on findings from the other (few) studies that have implemented octets, there should be one peak in force production (de Ruiter et al. 2004). Despite methodological differences between this thesis and other uses of the octet (i.e., training of alternative muscle groups, proximal nerve stimulation, and various training backgrounds) force production waveforms should be similar (de Ruiter et al. 2004; Balshaw et al. 2016). Hence, force traces for the octet measure in the present study were not consistent with previous findings and may have contributed to variability and invalid data. It is, therefore, tentatively concluded that muscle function did not change over the course of the study on a group level.

It is also possible that electrode placement for the octets changed between sessions and activated different regions of muscle fibers. Surface electrodes were placed on the muscle belly based on findings that motor neuron innervation primarily occurs at the center of the muscle (Masuda et al. 1985; Saitou et al. 2000). The use of electrodes with a larger surface area likely expanded the stimulated region. Yet, if the region of activation still did not cover all innervation zones, it is possible that electrode placement limited the volume of activated muscle fibers (Saitou et al. 2000; Enoka et al. 2020). Previous octet stimulation protocols activated the femoral nerve proximally at the femoral triangle (de Ruiter et al. 2004; Balshaw et al. 2016). However, more proximal electrical stimulation of the musculocutaneous nerve at Erb's point has not been shown to improve torque production compared to stimulation over the muscle and is more painful for the participant (Bergquist et al. 2011). Applying octet stimulations over the muscle belly could be the preferred protocol with more precise and consistent electrode placement (e.g., measuring from anatomical landmarks).

8.2 Neural adaptations

The StartReact test did not demonstrate any changes in reticulospinal adaptation. The StartReact effect remained unchanged in all groups for both arms, which is to be expected given the lack of strength gains in both training groups. The sustained training group exhibited a trend of decreasing StartReact effect with a large effect size, which cannot be explained by the resistance training program as changes in strength were not observed within the group.

When all participants were pooled together, the StartReact effect was observed pre- and post-training in both arms – VSRTs were significantly faster than VARTs – as expected. This comparison ascertained the validity of the StartReact test. The StartReact test was performed as expected compared to other studies in healthy humans, which also saw a significant reduction in reaction time between quiet and startling conditions (Valls-Solé et al. 1995; Baker & Perez 2017; Honeycutt et al. 2013; German & Baker 2021; German et al. 2023). Further, StartReact effect values and their variability in the present study (mean across groups and arms = 24.2 ± 8.8 ms, range: 10.6-31.9 ms) appear similar to previous studies that implemented the test in biceps (Figure 17; German et al. 2023; German & Baker 2021). The absence of changes in the StartReact effect is most likely attributed to the intervention, not to limitations in the method.

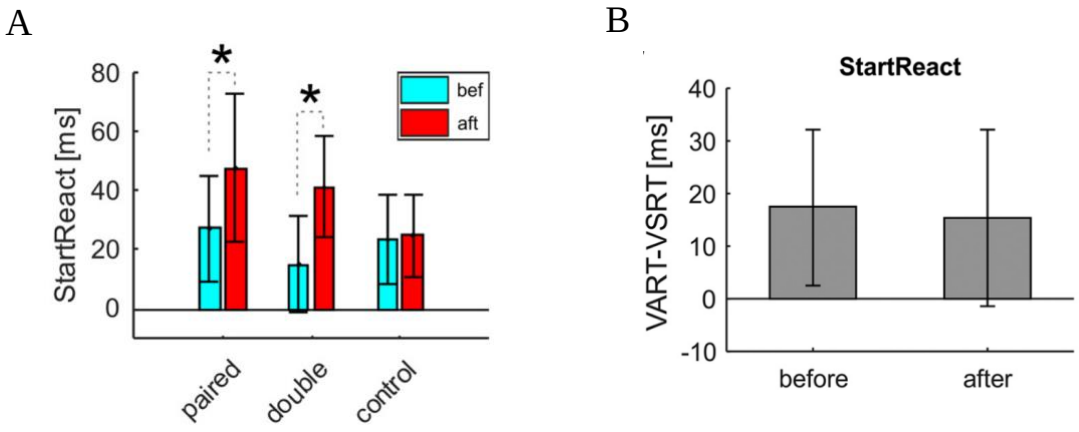

FIGURE 17. Graphical representations of StartReact effect data from studies that measured biceps brachii. Values were not reported in-text by the authors. (A) StartReact tests before intervention (cyan) and both control bars indicate comparable average StartReact effect values to the present study (German & Baker 2021). (B) StartReact effect values (VART-VSRT) before the intervention can also be used as a reference (German et al. 2023). *VART*, visual-auditory reaction time; *VSRT*, visual + startle reaction time.

Significant changes in normalized MEP size were not found in the PA or AP current orientations. Despite the lack of statistical significance, normalized MEP size values were greater among all participants in the explosive training group in both PA and AP orientations. Possible improvements in explosive strength for the right arm of the explosive training group coincides with the group's tendency for enlarged MEPs. Resistance training was expected to augment CST and RST excitability, presenting as increased normalized PA and AP MEP amplitudes. Meta-analysis data has reported resistance training has a moderate effect on MEP

amplitudes during voluntary contraction (Siddique et al. 2020). Studies that conducted a short-term (3-4 weeks, 9-12 total sessions) resistance training program targeting the biceps brachii observed MEP facilitation (Kidgell et al. 2010; Leung et al. 2013; Pearce et al. 2013). It should be advised that these studies were all conducted by the same research group, possibly biasing the results.

This justification that trends in MEP data in the explosive group could be attributed to strength gains, however, is weakened by the lack of data from the sustained group. Given that strength improvements were not observed in the sustained training group, comparison of MEP sizes between training groups would be useful in ascertaining possible physiological mechanisms behind the trend of greater MEP sizes in the explosive training group. Ultimately, a meaningful change in corticospinal or reticulospinal excitability cannot be concluded due to insufficient support from statistical analyses and only medium effect sizes.

MEP latencies and durations, cSPs, and aMTs yielded minimal evidence for neural adaptation. Trends toward decreased PA MEP latency and increased AP MEP duration were observed in the explosive training group with medium and large effect sizes, respectively. Shortened latency in PA MEPs, with no change in AP MEP latency, would suggest increased CST excitability. An increase in AP MEP duration would provide evidence for enhanced reticulospinal excitability but the change is not meaningful without a significant facilitation of MEP size. These theories also rely on speculation that AP stimulation emphasizes subcortical connections. Cortico-reticular activation via AP stimulation has not yet been validated in humans. Finally, there was a trend of greater PA aMT exhibited by all participants in the explosive group and the exhibited a large effect size, which would indicate reduced CST excitability. The inconsistencies in these results lead to inconclusive findings for changes in CST and RST function.

The LAS + TMS assessment exhibited suppression of the conditioned MEP in the majority of participants. No changes in MEP suppression were found in the control or training groups over time. Therefore, neural adaptations cannot be concluded from this test. Greater MEP suppression after resistance training would have suggested reduced reticulospinal excitability. Germann & Baker (2021) proposed that reticulo-cortical connections activated by LAS induce cortical suppression, which manifests in smaller MEPs. Based on comparisons to the literature, it is likely that these findings reflect physiological state and are not due to measurement error.

Average MEP suppression before and after training (76.2 ± 47.4% and 72.5 ± 36.1% of control MEPs, respectively) in the LAS + TMS protocol is similar to comparable studies (Figure 18; German & Baker 2021; Furubayashi et al. 2000), although variance appears to be greater in this study. The lack of evidence for neural adaptation observed from TMS output measures is consistent with strength and StartReact findings.

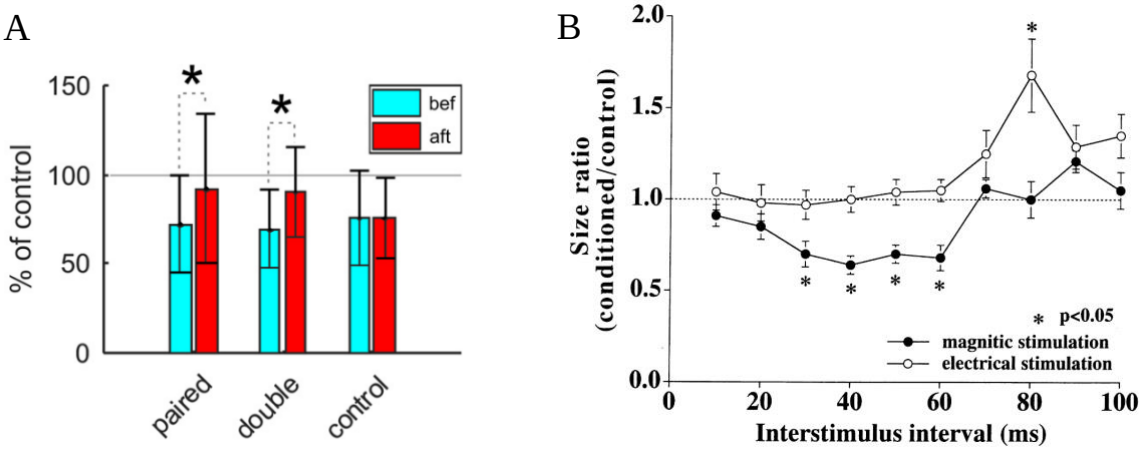

FIGURE 18. Suppression of the conditioned MEP found by comparable studies that implemented LAS + TMS protocols. Numerical values were not reported in-text by the authors. (A) German & Baker (2021) used the measure before and after an intervention. Both control group measures and all 'before' (cyan) measures can be used as a comparison. (B) Furubayashi et al. (2000) tested multiple LAS + TMS methods. Size ratio at 50 ms interstimulus interval, also used for this thesis, appears to be just above the smallest ratio reported at 40 ms interstimulus interval (0.64 ± 0.05). The authors only reported ratio values for the 40 ms interstimulus interval.

8.3 Limitations

An intervention study provides greater evidence because it allows for stronger evaluation of causality. Despite the scientific value of a randomized controlled trial, limitations in the methodology of the present thesis prevent us from drawing statistically supported conclusions regarding the effect of resistance training on the nervous system.

8.3.1 Limitations of the at-home resistance training device

There were a number of limitations to the at-home resistance training program. Of course, unsupervised training reduces control over the training sessions compared to a lab setting. The real-time force trace and target line features of the at-home training device attempted to improve the accuracy and reliability between contractions. The immediate automated uploading of training data, and email notices if training did not occur, held participants accountable to the training. It could also be argued that the flexibility of at-home training improves adherence because participants can adapt the training to their schedules rather than skipping the training entirely. In some cases, at-home training may have been too flexible. Sessions were done without a rest day in-between, which could have fatigued participants and impaired performance.

The use of a novel device with custom software carried a high element of risk. Device malfunctions were a major limitation of the resistance training program. After distributing the at-home training device, it became clear that data from MVC sessions were not being saved for subsequent training sessions. The participant would complete the MVCs, if applicable for that day, and the program would adjust target force lines for the training based on that day's best MVC. However, that would not be used for the following two training sessions before the next MVC session, thus, participants were training without accurate traces of their force production. The quality of the contractions and the progressive aspect of the training were compromised. This systematic error very likely impacted the effectiveness of the resistance training programs, especially the sustained-contraction group which relied on an accurate display of 70% MVC. The instruction for the explosive-contraction group to "pull as hard and as fast as you can" was less reliant on visual feedback. The importance of an accurate and consistent 80% MVC target for this group should still be emphasized, but a sufficiently self-motivation participant could complete the explosive training program without visual feedback. This speculation, that the MVC error more heavily impacted the sustained group, could explain the discrepancies in strength gains between the two training groups. Further, it was expected that greater improvements in MVC would occur in the sustained-contraction group compared to explosive-contraction (Balshaw et al. 2016). The lack of improvement in MVC of the sustained-contraction group is especially surprising and could be explained by problems with the device.

The device software was created to record force production during every contraction so the quality of the training could be observed, and feedback given to the participant. This system was not effective, and only the time of training completion was able to be determined. There were occasions where an error appeared at the end of training and it was not possible to determine how much of the training was done, thus, training quality assessment relied on accurate participant feedback. These errors made it difficult to determine the quality of contractions.

Additionally, if the adaptive MVC function worked as planned, the entire week's sessions would be altered based on that one day and a "poor" day could have influenced the whole week. It is impossible to completely control a resistance training study, especially one with at-home training. It was emphasized that participants should avoid any changes in their exercise routine, avoid activities involving heavy lifting, and train at a similar time of day. However, confounders that attenuate performance (psychological stress, poor sleep, poor nutrition, etc.) during an MVC session would affect the entire week. In a future iteration of the device, the reference MVC for target force lines should only be changed if the new MVC increases from the previous week. The device has great potential to be an effective tool for at-home resistance training upon refining of the software.

8.3.2 Methodological limitations

Only 38% of recruitment curves produced a sigmoid shape with a plateau in MEP amplitude at the highest stimulation intensities, resulting in omitting the measure from analyses. Without a plateau in MEP amplitude as stimulator output is increased, the output measures cannot be validated. Only three participants had valid recruitment curves in both experimental sessions and an additional four participants had one successful session. One possible explanation is high aMTs. All instances where the aMT was > 60% (n = 5) had invalid recruitment curves. These participants with higher aMTs could have had too few stimulation sets to demonstrate a sigmoid curve. A participant with an aMT of 66%, for example, would have only 4 sets of stimulations (66%, 76%, 86%, and 96% of maximum stimulator output). Another possibility, which applies to all invalid curves, is that maximal MEP amplitudes were reached in the final stages but required another increase in stimulator output to create a plateau. These explanations do not negate the fact that, based on the existing literature, our protocol should have yielded a sigmoid curve at lower aMTs. The plateau should occur around 170% aMT in an active muscle (Groppa

et al. 2012). Thus, participants with an aMT < 59% maximum stimulator output had the capacity to reach their maximum MEP amplitude, and yet some did not have a plateau.

Limitations to the M_{max} protocol caused exclusion of participants from the control (PA: n = 1; AP: n = 2) and sustained groups (PA: n = 3; AP: n = 3). The M_{max} protocol was not optimal for ensuring that maximal EMG output was reached. The method of 2 x 90 mA followed by 2 x 100 mA stimulations assumed that 90 mA was at least maximal, and 100 mA was supramaximal. Based on visual observation of the data, 90 mA was not maximal in four participants because the M-wave size increased from 90 to 100 mA. The remaining excluded data were too noisy, likely caused by poor electrode placement. The method could have been improved by implementing a systematic increase of stimulation intensity until the M-wave amplitude no longer increased, ensuring a supramaximal intensity was achieved. It is also possible that these limitations to the M_{max} protocol contributed to variability in normalized MEPs.

When comparing PA and AP MEPs, it should be considered that PA data was the average of 10 MEPs while AP data was the average of 20 MEPs. It would have been best practice to analyze the same sample sizes of the two current directions. The intraindividual variability of MEP data is well-known (Burke et al. 1995), and 20 trials have been recommended as preferable to 10 (Goldsworthy et al. 2016). Fewer trials also leave the data more easily manipulated by potential outliers during analyses.

The MATLAB program for MEP analyses automatically calculated the average MEP, then regions were marked manually. It could be argued that the MEP regions should be marked individually by the researcher and removed if they do not qualify as an acceptable MEP based on size, waveform, and timing. Marking MEP regions individually could provide more accurate data. Given the previously mentioned variability of MEPs, it is possible that stimulation intensities close to the aMT could fail to produce an acceptable MEP, which would go unnoticed with this analysis method. Although, more manual analyses could be vulnerable to human error and bias. Extrapolation of MEP regions were also used in the LAS + TMS protocol where regions for the average control MEP were manually marked and applied automatically to the conditioned MEP. This approach is more objective by standardizing the duration of the analyzed MEP area.

The limitations of statistical analyses should be heavily considered when drawing conclusions from this thesis. The sample sizes alone led to initially excluding parametric testing. However, the samples were so small in this study that Wilcoxon non-parametric tests yielded a Type II error when $n < 5$, with an alpha level of 0.05. The loss of statistical power with smaller sample sizes was compounded by the diminished statistical power from a non-parametric test and likely caused the decreased probability of detecting a significant effect (Morgan 2017).

Parametric tests (t-tests) were ultimately used for statistical analyses, but the limitations of this method are extensive for the present study. Equal variance and normal distribution of the data were checked prior to any parametric testing. Although, both assumptions are highly influenced by sample size (Morgan 2017). Small samples compromise use of the central limit theorem because it is difficult to determine normality (Pagano et al. 2022, 192-193 & 297). The statistical power of parametric tests is also limited by small samples (Pagano et al. 2022, 241). Further, when corrected for multiple comparisons, the adjusted alpha level of 0.0167 ($\alpha = 0.05/3$) left all comparisons insignificant. Given these limitations, analyses were minimized to within-group comparisons using t-tests. To summarize, the limitations of statistical analyses are extensive and should be appreciated when interpreting results from this study.

8.4 Future research

There is clearly still a need for more resistance training intervention studies using TMS to probe CST, RST, and intracortical circuits. This study was unable to answer whether the RST contributes to neural adaptations to resistance training, but promising findings in primate models should motivate researchers to test this hypothesis in humans (Glover & Baker 2020).

As the role of the reticulospinal system is quantified, it should not be assumed that corticospinal influence is fully understood (Kidgell et al. 2017; Siddique et al. 2020). Researchers have struggled to find trends in the existing literature targeting intracortical and corticospinal adaptation to resistance training. This is in large part due to the variation in TMS methods and output measures. The TMS protocols used for this study, as well as many others, measure adaptations to the entire motor pathway, thus, the region of adaptation is difficult to ascertain. Corticospinal investigations have also implemented different training types, targeted an assortment of muscle groups, and recruited participants of various training status (Kidgell et al. 2017; Siddique et al. 2020). Further reticulospinal studies should reflect on the limitations in

corticospinal research and implement refined and standardized methods to understand the mechanisms behind motor pathway adaptations to resistance training. Implementing protocols such as SICI, long-interval cortical inhibition (LICI), ICF, cervico-medullary MEPs (CMEPs), or TMS paired with electroencephalography (EEG) could help identify the level of adaptation, as well as whether those changes are within excitatory and/or inhibitory synapses.

This thesis specifically investigated responses in the biceps brachii in the dominant arm after training one isometric contraction, but many other coactivations involved in resistance training could be addressed. At this point, most studies have only measured the neurophysiological responses of one muscle to a training program (Siddique et al. 2020). It would be interesting to investigate neural adaptations of antagonistic and stabilizing muscles. The extent of CST- and RST-mediated adaptations could be determined in those muscles as well. Motor pathway contributions to cross-education could also be examined by isolating training to one arm and comparing the neurophysiological responses on both sides. Simultaneous activity in these other muscle groups could be particularly relevant to the RST given its role in posture and bilateral motor outputs (Buford 2009).

9 CONCLUSION

The present study aimed to ascertain CST and RST adaptations to resistance training, and how the tracts may differ in response to sustained- vs. explosive-contraction training. The 6-week resistance training programs did not induce significant strength gains, with only trends toward improvement in RFD and MVC in the explosive training group. The reduced statistical power from small sample sizes could have masked notable improvements in maximal and explosive strength. However, it can only be speculated that the explosive training group exhibited strength gains without statistical evidence to substantiate the claim. Limitations to the resistance training device that likely had a greater impact on the sustained training group could explain the discrepancy in strength gains between the training groups.

Minimal neural adaptations were found and any trends lacked clear evidence for increased excitability in either tract. Comparison of neurophysiological data to other studies indicates that the tests were valid and the lack of observed changes in CST and RST function can likely be attributed to the ineffective resistance training programs. This thesis could not be concluded whether resistance training causes adaptation in the CST or RST, and therefore, it could not be determined whether neural adaptations are training type-specific.

Despite these null results, it is important to continue investigating corticospinal and reticulospinal contributions to neural adaptation to resistance training. Currently, conclusions from studies of intracortical and CST short-term adaptations to resistance training are equivocal (Kidgell et al. 2017; Siddique et al. 2020). Nonhuman primate models have revealed RST function in the upper-limb (Baker 2011), reticulospinal coding for force production during resistance training (Glover & Baker 2022), and M1 and RST adaptations to short-term resistance training (Glover & Baker 2020). Previous literature has justified further examination of these motor pathways with a resistance training intervention in humans (Atkinson et al. 2022).

This new appreciation of reticulospinal functionality can have applications across many sub-disciplines of neurophysiology, from resistance training adaptations to clinical applications in treatment of motor function after spinal cord injury or stroke (Akalu et al. 2023). Therefore, it is important to continue investigating the role of reticulospinal motor functioning in these contexts and, potentially, how to induce plasticity for performance gains and clinical treatments.

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