

Investigating a novel exercise training strategy on neuromuscular health

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Abbreviations

1-RM	1-repetition maximum
AA	Amino acids
ACh	Acetylcholine
AChE	Acetylcholinesterase
AP	Action potential
ATP	Adenosine triphosphate
BB	Biceps brachii
BMI	Body mass index
Ca^{2+}	Calcium ions
CE	Cross education
CFT	Complex force tracking
CMAP	Compound muscle action potential
CMJ	Counter-movement jump
CoV	Coefficient of variation
DF	Dorsiflexors
DQEMG	Decomposition-based quantitative electromyography
EDB	Extensor digitorum brevis
EF	Elbow flexors
EMG	Electromyography
ET	Essential tremor
EWGSOP	European Working Group on Sarcopenia in Older People
FDI	Flexor dorsal interosseus
FS	Force steadiness

iEMG	Intramuscular electromyography
IPAQ	International physical activity questionnaire
K^+	Potassium ions
KE	Knee extensors
MC	Motor control
MCT	Motor control training
MG	Medial gastrocnemius
MPB	Muscle protein breakdown
MPS	Muscle protein synthesis
MS	Multiple sclerosis
MU	Motor unit
MUNE	Motor unit number estimate
MUP	Motor unit potential
MUPT	Motor unit potential train
MVC	Maximal voluntary contraction
Na^+	Sodium ions
NF	Near fibre
PA	Physical activity
PF	Plantar flexors
PIS	Participant information sheet
RET	Resistance exercise training
RF	Rectus femoris
RFD	Rate of force development
RMP	Resting membrane potential
SD	Standard deviation

sEMG	Surface electromyography
SKM	Skeletal muscle
sMUP	Surface motor unit potential
SR	Sarcoplasmic reticulum
SSR	Spinal stretch reflex
TA	Tibialis anterior
TMS	Transcranial magnetic stimulation
US	Ultrasound scans
VL	Vastus lateralis
VM	Vastus medialis

1. Introduction

1.1. Skeletal muscle: A brief introduction

Skeletal muscle (SKM) accounts for approximately 40% of total body mass in healthy adults (McLeod et al., 2016). The preservation of SKM across the human lifespan not only allows for maintenance of physical independence, but also allows for the maintenance of whole-body metabolic health (Wilkinson et al., 2018) and protection from metabolic morbidities such as insulin resistance and subsequent development of diabetes (Brook et al., 2016). SKM is known for its importance in posture, breathing and locomotion (McLeod et al., 2016), with a remarkable ability to adapt to (e.g.) endurance and resistance type exercise (Brook et al., 2016), both of which lead to extreme distinct changes in an individual's phenotype. Importantly, however, the role of SKM is not solely limited to its force generating capacities. For example, SKM is responsible for the majority of post-prandial glucose disposal and plays a central role for whole-body protein metabolism (Wolfe, 2006), with the additional ability to liberate large pools of amino acids (AA) in conditions of fasting or stress (Brook et al., 2016).

Focusing on SKM mass, consistent levels are typically observed during the early years of life (with the exception of diseased states) until ~50 years where muscle begins to atrophy (Brook et al., 2016). This age-related loss of SKM mass is termed "sarcopenia" (Rosenburg, 1997), a muscle disease that presents due to adverse muscle changes characterised through low muscle quantity, quality and strength, hence predisposing an individual to an increased likelihood of physical

disability, falls/fractures and mortality (Cruz-Jentoft et al., 2019). Longitudinal studies report that individuals aged ~75 years exhibit muscle mass declines of 0.80 – 0.98% per year in men and 0.64 – 0.70% per year in women (Mitchell et al., 2012). Importantly, muscle strength (a commonly used proxy measure to assess muscle function) is lost more rapidly than muscle mass, with declines of 3 – 4% per year in men and 2.5 – 3% per year in women aged ~75 years (Mitchell et al., 2012). For example, Izquierdo and colleagues demonstrated older men (60 – 74 years) had significantly lower maximal unilateral knee extensor (KE) strength, during both isometric and concentric muscle contractions, compared to middle-aged (35 – 46 years) men (Izquierdo et al., 1999*b*). Sex differences in muscle mass and strength decline are not only apparent in aged muscle, with young individuals also showing variations in both absolute (33.0 ± 5.3 *vs.* 21.0 ± 3.8 kg; males *vs.* females) and relative (38.4% *vs.* 30.6%; males *vs.* females) terms (Janssen et al., 2000) with respect to muscle mass. Such differences in SKM appear to be regional, as although males have significantly greater SKM in both the lower (18.1 ± 3.1 kg) and upper (14.1 ± 2.6 kg) body compared to females (lower: 12.2 ± 2.5 kg; upper: 8.4 ± 1.8 kg), this sex difference is less in the lower (33%) compared to upper (40%) body (Janssen et al., 2000). Sex differences in SKM distribution across the body are also consistent with the sex differences in muscle strength, with discrepancies in lower body strength (~30%) being smaller than observations for upper body strength (~50%; Janssen et al., 2000).

It is beyond the scope of this thesis to cover all aspects of SKM involvement with respect to maintaining whole-body health. Despite this, health and

maintenance of SKM muscle should be considered as a whole and not compartmentalised due to undeniable links between many health-related aspects directly related to SKM (e.g. muscle mass and insulin resistance; Wilkinson et al., 2018). As such, the aim of maintaining SKM "health" (i.e. mass and function) throughout the life course should be viewed as a method to improve whole-body health, maximise quality of life and prolong independence, in the absence of disease.

1.2. Structure of skeletal muscle and mechanisms of muscle contraction

The structure of SKM is far from simple (see Figure 1.1. for illustration). Essentially, the muscle is made from thousands of layers of proteins; the most superficial being the muscle "body" created from muscle fascicles, and the deepest being the myofibrils which are subsequently made from thousands of myofilaments (naming actin and myosin). It is these myofilaments which house the contractile elements of the muscle, sarcomeres (see Figure 1.1.), which are uniform in appearance and comprised of actin, myosin, nebulin and titin (Marieb, 2005, p. 248). Specifically, actin (thin) filaments, are anchored to the Z discs each end of a sarcomere by nebulin and contain regulatory proteins, troponin and tropomyosin, which are essential to allow muscle contraction (Marieb, 2005, p. 250). Tropomyosin provides rigidity to actin and also blocks actin's active sites when the muscle is relaxed to prevent a state of tetanus, whereas troponin is a three-polypeptide complex which allows for the binding of actin, tropomyosin and calcium ions (Ca^{2+}; Marieb, 2005, p. 250). Myosin (thick) filaments, contain a tail and two globular heads which bind to actin to form a "crossbridge" during contraction (Huxley, 1969). Despite the subsequent

focus on muscle contraction below, the role of titin should not be overlooked. Titin is vitally important in the process of muscle relaxation, with its two main roles being: 1) holding myosin filaments in place, thus maintaining organisation of the A band and, 2) assisting the muscle cell to spring back into shape after contraction (Marieb, 2005, p. 251). The integration of these myofibrillar proteins is, therefore, of utmost importance to understand as a whole with respect to the process of SKM contraction and subsequent relaxation.

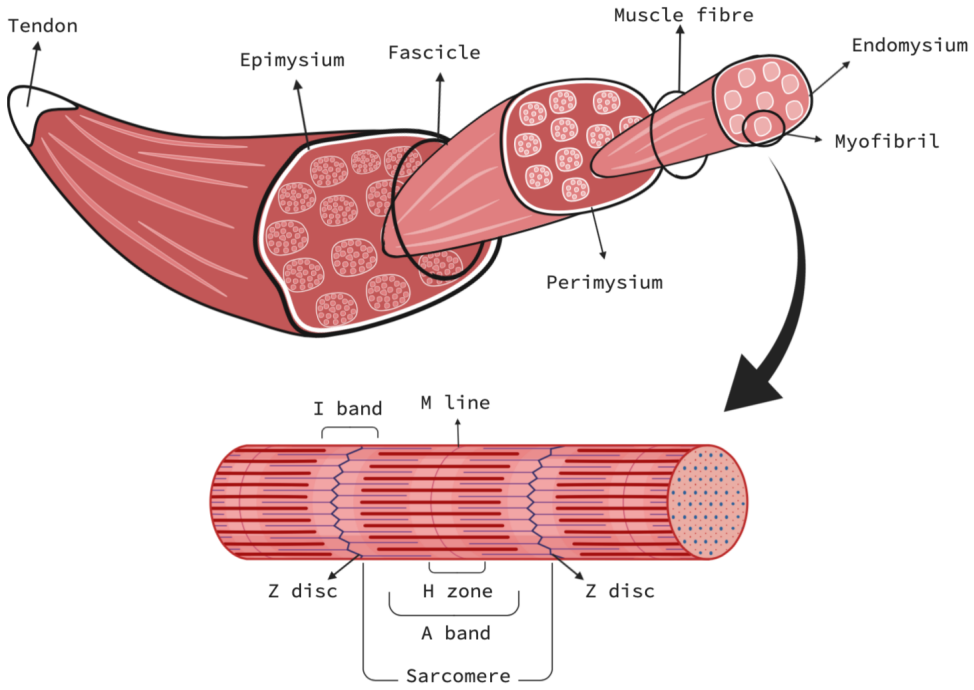


Figure 1.1. *Illustration of skeletal muscle structure. Created in Biorender.*

Simply put, the process of SKM contraction (termed the sliding filament theory; Huxley, 1969) occurs by the sliding of the myofilaments, actin and myosin, past each other to create an overlap of a greater degree than in a relaxed state, thus generating muscle shortening. Briefly, the binding of Ca^{2+} to troponin, released from the sarcoplasmic reticulum (SR) in response to an action potential (AP),

allows troponin to undergo a conformational change, thus removing tropomyosin from actin active sites. This subsequently allows for excitation-contraction coupling (Allen et al., 2008), with myosin globular heads to binding to actin, forming a crossbridge (Huxley, 1969; Marieb, 2005, p. 258). Interestingly, from examining muscle cross-sections, the arrangement of actin and myosin within myofibrils seems to be in a hexagonal lattice (Huxley, 2004; see Figure 1.2.), allowing for optimal crossbridge formation to generate force between the filaments. Through the rapid hydrolysis of adenosine triphosphate (ATP), myosin detaches and rebinds to actin multiple times in a ratchet style motion (crossbridge cycling) allowing the muscle to shorten (Huxley, 1969). Importantly, when Ca^{2+} is returned to the SR via active transport, muscle contraction ceases, therefore allowing the resting state of the contractile material to be restored (Huxley, 1974).

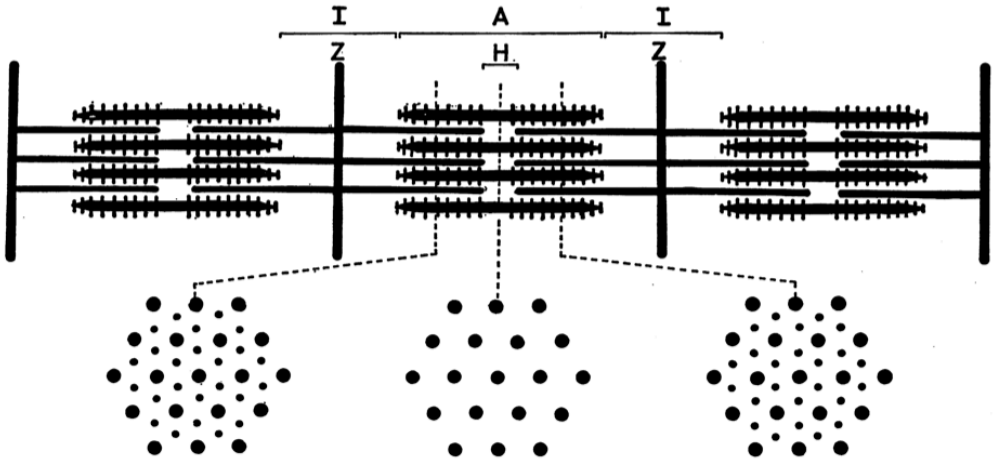


Figure 1.2. *Image taken directly from Huxley (1969). Diagrammatic representation highlighting differing hexagonal lattice arrangements of actin (smaller circles) and myosin (larger circles) within a sarcomere.*

Importantly, the process of SKM contraction would not be possible without involvement of the nervous system; put simply, SKM would not be able to function without neural input. The generation and propagation of APs and the role of the SR with respect to Ca^{2+} release/re-uptake, are of vital importance to achieve successful muscle contraction and relaxation. Therefore, understanding the role of the neuromuscular junction (NMJ) and APs is essential to develop insight into muscle contractile function.

Skeletal muscle cells are stimulated by motor neurons. The motor neuron cell body resides in the ventral horn of the spinal cord and extends an axon which branches to form an NMJ at innervation sites with individual muscle fibres (Piasecki et al., 2016*a*). Muscle excitability is dependent on regulation of normal axonal resting membrane potential (RMP; ~ -70mV) which allows for neuromuscular transmission of APs to enable muscular contraction (Allen et al., 2008). When the internal axonal membrane potential increases past threshold levels (~ -55mV), depolarisation occurs thus generating an AP which propagates down the axon to reach an NMJ, where the AP synapses with the muscle sarcolemmal membrane (Marieb, 2005, p. 253); subsequently leading to skeletal muscle contraction. The process and involvement of the NMJ to initiate SKM contraction is illustrated in Figure 1.3. Briefly, when the AP reaches the NMJ, voltage-gated channel proteins open allowing the influx of Ca^{2+} from extracellular fluid. This leads to vesicles of acetylcholine (ACh) translocating and fusing to the axonal membrane, allowing for ACh to be expelled into the synaptic cleft via exocytosis (Marieb, 2005, p. 254). ACh diffuses across the cleft and binds to the ACh receptor located on the sarcolemmal membrane,

allowing for a rapid influx of sodium ions (Na^+) and efflux of potassium ions (K^+) across the membrane. Consequently, AP generation occurs with rapid sarcolemmal and tubular system propagation to trigger Ca^{2+} release from the SR (Allen et al., 2008). Due to this propagation and the subsequent breakdown of ACh by acetylcholinesterase (AChE; located in the synaptic cleft and on postsynaptic membranes), the muscle fibre is synchronously activated, leading to successful muscle contraction (Allen et al., 2008).

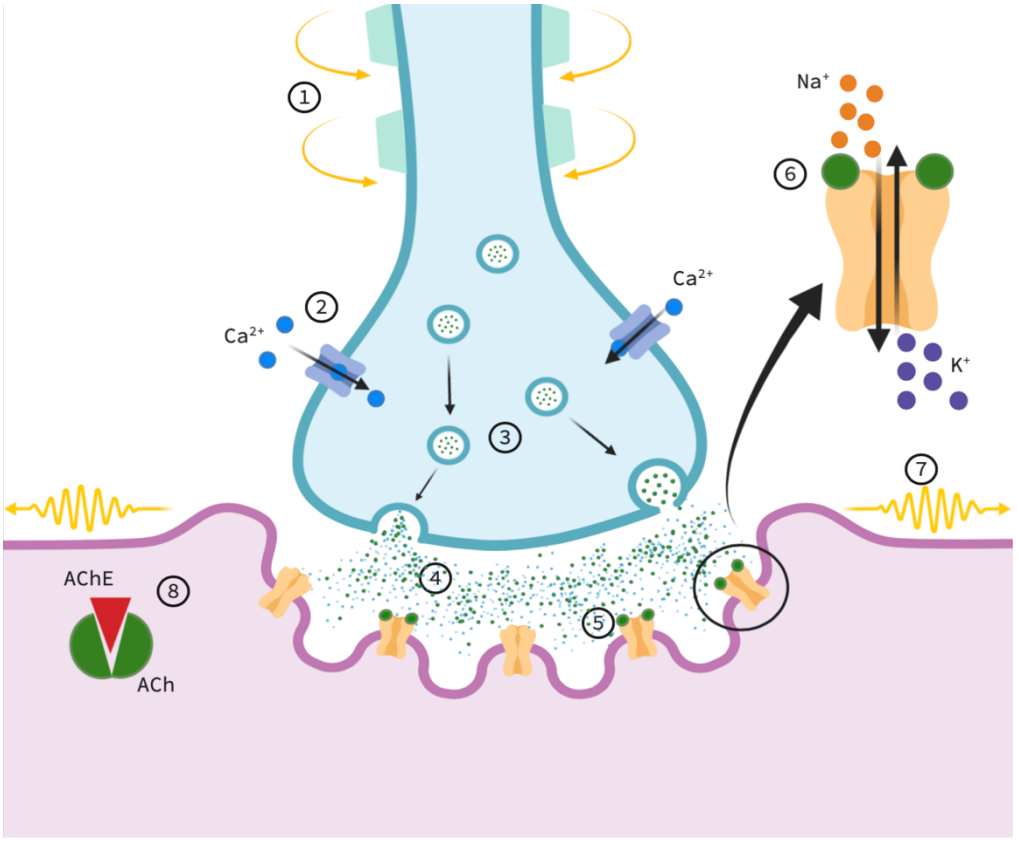


Figure 1.3. *Illustration of neuromuscular junction (NMJ) and action potential (AP) generation to stimulate muscle contraction. 1) AP arrives at NMJ; 2) voltage-gated channel proteins open, causing an influx of calcium ions (Ca^{2+}) into pre-synaptic bulb; 3) vesicles filled with acetylcholine (ACh) translocate and fuse to NMJ membrane; 4) ACh expelled into synaptic cleft via exocytosis; 5) ACh binds to receptors on sarcolemmal membrane; 6) binding of ACh causes an influx of sodium ions (Na^+) and efflux of potassium ions (K^+); 7) AP generated on sarcolemmal membrane which propagates along the whole muscle fibre; 8) breakdown of ACh via acetylcholinesterase (AChE). Created in Biorender.*

As described above, the integration of the SKM and nervous systems are extremely important for the conduction of muscle contraction and as such must be considered in unison. Subsequently, the integration and coordination of these systems are thought to be inextricably linked, as suggested in a recent review (Wilkinson et al., 2018), to maintain muscle health throughout life; and as such will be focused on throughout the rest of this thesis.

1.3. Impact of ageing on the muscular system

Population demographics worldwide are ageing rapidly with continuous advancements in healthcare and knowledge of optimal nutrition leading to increased lifespan (Wilkinson et al., 2018). Predictions suggest that by 2050, the global population of those aged over 65, 85 and 100 years is set to increase by 188%, 551% and 1004% respectively (McLeod et al., 2016). An elevated ageing populace will undoubtedly lead to additional strains on worldwide healthcare systems due to heightened prevalence of chronic diseases, including sarcopenia (McLeod et al., 2016; Wilkinson et al., 2018). Resultingly, knowledge of this has led to attempts to limit the progression of such diseases through both pharmacological and/or lifestyle interventions (Wilkinson et al., 2018). For instance, lifestyle changes may include increased physical activity (PA), which seemingly declines with ageing (McPhee et al., 2016), and dietary modifications such as heightened daily protein intake (Bauer et al., 2013).

Despite development of the interventions briefly mentioned above, muscle mass ultimately declines with age, with this process being termed sarcopenia (Rosenburg, 1997). Although there is a plethora of evidence surrounding

sarcopenia (see Mitchell et al., (2012) for a narrative review), concurrently, there is no agreed universal definition, principally due to a lack of diagnostic criteria (Cruz-Jentoft et al., 2010). It is important to note here, that there is no one sole contributor to the progression of sarcopenia, more of a combination and integration of multiple factors such as sedentarism, impaired AA sensing, inflammation, lipid infiltration and increased reactive oxygen/nitrogen species (Wilkinson et al., 2018). Indeed, only last year the European Working Group on Sarcopenia in Older People (EWGSOP) stated that "sarcopenia is a muscle disease that occurs due to adverse muscle changes throughout the lifespan" (Cruz-Jentoft et al., 2019). In addition to this, the EWGSOP also recently updated their sarcopenia definition to include low muscle strength as the primary parameter of sarcopenia; with low muscle quality, quantity and strength suggesting severe levels of sarcopenia (Cruz-Jentoft et al., 2019). As stated previously, in individuals aged ~75 years, muscle mass is lost at a rate of 0.64 – 0.98% per year, with muscle strength being lost at a greater rate than mass declines (2.5 – 4% per year; Mitchell et al., 2012). Due to this unequal decline in muscle mass and strength, the term dynapenia was derived to describe the age-related declines of muscle strength and power (Clark et al., 2008; Manini & Clark, 2012), with the terms sarcopenia and dynapenia being subsequently proposed to be considered separately, as the loss of muscle strength is only partially explained by declines in muscle mass (Manini & Clark, 2012). Although a disparity still remains between declines in muscle mass and strength, in light of the most recent updated definition from EWGSOP (Cruz-Jentoft et al., 2019), the use of sarcopenia encompasses concurrent declines of both muscle mass and strength; thus, steering away from the separate definition of dynapenia.

Considering the above, it is no surprise that age-related muscle wasting, and loss of function has both severe physiological and psycho-social problems including; loss of independence, depression, increased risk of frailty and falls, sedentarism (physical inactivity) and increased risk of all-cause mortality (Wilkinson et al., 2018). As such, the scientific underpinning of age-related functional declines is both important and timely to understand, with the potential to aid development of countermeasures to ultimately improve an individual's quality of life. A recent review by Wilkinson et al., considers two of the main contributors affecting the progression of age-related decline in muscle mass and function; anabolic resistance (desensitising of a muscles ability to respond to key anabolic cues; namely nutrition (protein) and/or exercise) and muscle fibre loss, subsequently leading to motor unit (MU) remodelling (Wilkinson et al., 2018). Extensive scientific literature provides knowledge that the maintenance of muscle mass is regulated by the dynamic relationship between muscle protein synthesis (MPS) and muscle protein breakdown (MPB), leading to a typical protein turnover rate of 1 - 2% per day in young healthy individuals (Atherton et al., 2010, 2016; Breen et al., 2013; Wall & van Loon, 2013). In aged muscle, the anabolic response to such stimuli (feeding and exercise) seems to be depressed, resulting in reduced MPS response (Atherton et al., 2010; Wall et al., 2015) and suppressed inhibition of MPB (Greenhaff et al., 2008); thus, leading to muscle mass decline. Additionally, as muscle function is achieved as a combination of muscle size and neural mechanisms (Campbell et al., 2019), the contribution of muscle fibre loss and subsequent MU remodelling (Piasecki et al., 2016*a*) should be equally considered, as it is likely that neuromuscular mechanisms and loss of

MUs may explain the additional deficits in age-related functional decline not explained by muscle atrophy (Piasecki et al., 2016*a*). Due to the scope of this thesis, from here onwards, the main focus will be surrounding alterations to the neuromuscular system with age and potential attenuative strategies to aid healthy ageing.

1.4. The ageing neuromuscular system

The human MU is the smallest functional component of the neuromuscular system, consisting of a single alpha motor neuron and all of the muscle fibres it subsequently innervates (Sherrington, 1925). The motor neuron cell body itself is located in the ventral horn of the spinal cord and extends an axon that branches to form NMJs at innervation sites within individual muscle fibres (Piasecki et al., 2016*a*). Importantly, within a healthy young MU, there is no "mixing" of phenotypic characteristics. Therefore, a MU displays the same properties (e.g. type I or type II) and is contracted in an all-or-none manner (Piasecki et al., 2016*a*). It is rare that muscle fibres of the same MU are immediately adjacent to each other due to MU territories spanning several centimetres in length and 5 – 10 mm in depth within large limb muscles (Buchthal et al., 1959). For example, in human medial gastrocnemius (MG), MUs seem to extend no less than 1 cm and no greater than 4 cm along the longitudinal axis (~25 cm) of the muscle; thus, displaying small MU territories (Vieira et al., 2011). Additionally, it is known that approximately two-dozen MUs with an innervation ratio of ~500 – 2000 fibres spanning across a muscle cross-sectional depth of 5 – 7 mm and 7 – 10 mm are found in the upper and lower limb respectively (Buchthal et al., 1959). This arrangement allows for the distribution of forces across relatively large areas of muscle to aid with successful contraction (Piasecki et al., 2016*a*).

Although it is difficult to provide specific innervation ratios, it is known that they depend on the role and size of the muscle (Piasecki et al., 2016*a*), with larger limb muscles containing up to thousands of MUs and millions of muscle fibres (Tomlinson & Irving, 1977; Lexell et al., 1988).

Over the past five decades, there have been developments in methodologies to study human MUs with the aim to understand the processes affecting the neuromuscular system, including ageing. As summarised by Piasecki and colleagues, estimations of MU and muscle fibre numbers have been limited to post-mortem studies (the gold standard) and the use of electromyography (EMG), which facilitates detailed investigations of MU function, recruitment patterns and estimates of MU numbers in individual muscles (Piasecki et al., 2016*a*). Identified by Tomlinson and Irving, up until ~60 years of age, estimates of motor neuron cell bodies (located in the lumbosacral spinal cord from 47 deceased specimens aged 13 – 95 years) remained relatively constant with declines evident after this point (Tomlinson & Irving, 1977); a similar timepoint to the occurrence of age-related muscle mass declines (Brook et al., 2016). Lexell et al., further evidenced to this through reporting vastus lateralis (VL) muscle from older adults to be 18% smaller than young muscle (Lexell et al., 1983). This was solely attributed to the significant decline in the number of myofibres in old (364,000) compared to young (478,000) muscle (Lexell et al., 1983). Furthermore, Lexell et al., highlighted a 40% age-related reduction in muscle size in those aged 20 to 80 years which was largely associated with a 39% reduction in the number of fibres (Lexell et al., 1988). However, atrophic fibres were also evident, thus reduction of muscle fibre size in conjunction with

fibre loss needs to be examined concurrently to advance knowledge in age-related functional decline. With anatomical count studies being rare for obvious reasons, mean fibre cross-sectional area (CSA) and total muscle CSA can be used to provide estimates of MU and muscle fibre numbers. Through conducting a 12-year longitudinal study, Frontera et al., reported quadriceps CSA to decline by 14.7% in those aged 65 to 77 years, which was attributed again to muscle fibre loss as no significant declines were evident in individual muscle fibre CSA (Frontera et al., 2000). In comparison, McPhee and colleagues observed a reduction of 28% in old VL CSA compared to young, which was attributed to, almost equivocally, reduction in type II fibre CSA and muscle fibre loss (McPhee et al., 2018). When examining biceps brachii (BB), Klein et al., found minimal differences in young (253,000) and old (234,000) fibre numbers; suggesting there may be discrepancies in the effect of age on atrophy processes depending on the muscle of interest (Klein et al., 2003). Such evidence, however, suggests that decreases in muscle size cannot solely explain the reduced muscle functional capacity; thus, suggesting substantial neuromuscular remodelling with age has a role in these detrimental functional declines (Wilkinson et al., 2018).

The use of EMG, both surface (sEMG) and intramuscular (iEMG), has allowed further advancement in understanding the ageing neuromuscular system and consequential remodelling processes (described below). Initially, percutaneous electrical stimulation techniques were adopted to innervate nerve branches, enabling a surface compound muscle action potential (CMAP) to be recorded via a surface electrode (sEMG) over the muscle. Derivation of a motor unit

number estimate (MUNE) occurred when a calculated average motor unit potential (MUP), from all sampled MUPs generated involuntarily from low level percutaneous electrical stimulation, was divided into a maximal CMAP (Piasecki et al., 2016*a*, 2018*b*). Despite this technique being repeatable and reliable as shown by Piasecki and colleagues, inconsistent activation of different MUs with similar activation thresholds (termed alternation) and/or the cross-contamination of muscles sharing the same neural pathway provides some difficulties with this technique (Piasecki et al., 2016*a*, 2018*b*). Consequently, the use of indwelling needles via iEMG to record MUPs during low to moderate isometric contraction intensities was developed to overcome this problem (Piasecki et al., 2016*a*, 2018*b*). The methodology of iEMG is described in detail elsewhere (Piasecki et al., 2016*a*, 2018*b*), but briefly, the use of iEMG enables the recording of a small proportion of muscle fibres within individual MUs, with sampled MUPs used to "trigger" the corresponding surface-recorded MUP to generate a surface MUP (sMUP): a technique known as "spike triggered averaging" (Piasecki et al., 2016*a*). Importantly, both of these techniques have been influential in demonstrating MU loss and remodelling with ageing *in vivo* (Piasecki et al., 2016*a*).

Through using incremental stimulation, Campbell et al., reported MUNE of extensor digitorum brevis (EDB) to remain fairly constant until the age of 60 years (Campbell et al., 1973); similar to that displayed by Tomlinson and Irving (Tomlinson & Irving, 1977). Furthermore, individuals aged 75 years and over seemed to display less than 50% of the MUs compared to young counterparts, with some of the very old subjects having less than 10% of their MUs remaining

(Campbell et al., 1973). The development and use of EMG techniques has consistently shown older individuals to have a reduced MUNE (McNeil et al., 2005) but larger MUPs (Hepple & Rice, 2016; Piasecki et al., 2016*a*) compared to young individuals. Larger MUPs are evident in several muscle groups including VL (+25%; Piasecki et al., 2016*c*) and tibialis anterior (TA; +43%; Piasecki et al., 2016*b*). This initially seems counterintuitive due to the reduction in MUNE with age. However, the underpinning mechanisms of these larger MUPs, is highly likely due to reinnervation of denervated fibres from a nearby axon (Wilkinson et al., 2018) in an attempt to preserve muscle mass; known as MU remodelling (Piasecki et al., 2016*a*) (Figure 1.4.). Further work from Piasecki and colleagues, highlighting a crucial advancement in the literature, found that sarcopenic individuals had significantly smaller MUPs than the MUP size of non-sarcopenic (+26%) and pre-sarcopenic individuals (+41%) (Piasecki et al., 2018*a*); thus, not following the "trend" of increased MUP size with age. Instead the authors conclude there is a failure to expand MU size, therefore, suggesting failure to reinnervate denervated fibres distinguishes sarcopenic from non-sarcopenic older men, with excessive fibre loss evident when reinnervation is no longer able to occur (Piasecki et al., 2018*a*).

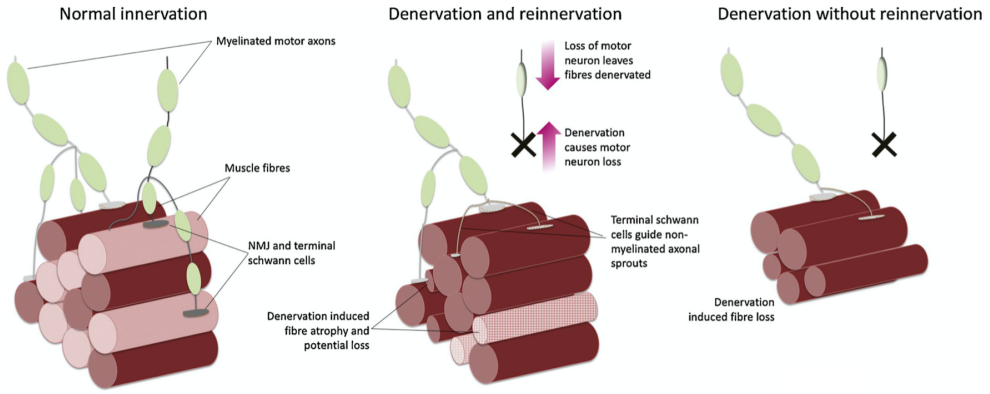


Figure 1.4. *Image taken directly from Wilkinson et al., (2018) summarising the motor unit (MU) remodelling process. The denervation and reinnervation process (middle panel) prevents excessive fibre atrophy and potential loss, with no reinnervation leading to the loss of muscle fibres (right panel).*

Recent evidence has focussed on the role of lifelong exercise as a preventative measure for the age-related decline in muscle wasting (McKendry et al., 2018) and MU loss (Power et al., 2010; Piasecki et al., 2019). Despite there being PA guidelines for older adults (150 minutes per week of moderate-to-vigorous PA plus some form of resistance exercise for the major muscle groups at least twice a week), we know that the proportion of older adults meeting these guidelines is strikingly low (McPhee et al., 2016), likely due to the factors that limit PA uptake and adherence across the population (e.g. lack of time, dislike of exertion, facilities access; McPhee et al., 2016), as well as the increased prevalence of reduced independence and functional impairments (McKendry et al., 2018). A recent systematic review conducted by McKendry and colleagues, focused on the influence of lifelong exercise in master athletes aged 60 years and over, who would have usually begun to experience age-related declines in physical function (McKendry et al., 2018). The authors highlight that through the continuation of endurance and strength/power type exercise training, cardiovascular fitness and muscle strength respectively can be maintained and

act to attenuate the age-related declines seen in untrained age-matched individuals (McKendry et al., 2018); therefore, suggesting that those who continue lifelong exercise, maintain functional independence and thus a good quality of life. When focussing on the potential preservation of MUNE in master athletes, Power et al., highlight that MU number did not differ between master runners (140 ± 53 MU) and young individuals (150 ± 43 MU) in TA, with old age-matched sedentary controls showing a reduced MUNE (91 ± 22 MU) (Power et al., 2010). Conversely, Piasecki and others reported that both older individuals (71 ± 4 years) and master athletes (69 ± 3 years) had reduced MUNE values of 45% and 40% respectively compared to young counterparts, with MUP size (recorded used iEMG) greater in both the old (43%) and master athletes (53%) compared to young (Piasecki et al., 2016*b*). Further work by Piasecki and colleagues highlights that MU number was not preserved in the VL of older athletes, and MUP size was again larger in VL for all older individuals compared to young, with greater MUP size in old athletes compared to old controls (Piasecki et al., 2019). This therefore suggests that lifelong training does not, in fact, attenuate age-related loss of MUs, hence countering the findings of Power and colleagues (Power et al., 2010). Despite this contentious area, MUP size seems to be consistently larger in master athletes compared to sedentary age-matched controls (Piasecki et al., 2016*b*, 2019), suggesting that lifelong exercise may facilitate more successful reinnervation of denervated fibres; thus aiding greater success of MU remodelling with age to preserve function, although further evidence is needed to confirm this.

1.5. The importance of motor control

Muscle strength, a function of muscle size and neural mechanisms (Campbell et al., 2019), is important for both the success and completion of tasks associated with daily living (Carroll et al., 2001). Muscle force generated for these daily tasks (e.g. walking/getting out of a chair), is conducted by multiple muscles in unison rather than those in isolation (Carroll et al., 2001). Consequently, intramuscular factors, neural capacity and levels of muscle coordination are all required for efficient and successful movement (Carroll et al., 2001). Therefore, with the age-related declines in the neuromuscular system (as highlighted in section 1.4.), completion of daily tasks becomes increasingly difficult due to the subsequent reduction in muscle functional capacity (Wilkinson et al., 2018). One aspect which should be considered to change with ageing is an individual's level of motor control (MC) (Enoka et al., 2003). The term MC encapsulates multiple factors including, for example, posture, muscle coordination and sensorimotor integration (Carroll et al., 2001). It is important to note here that this thesis only focusses on one aspect of MC (the ability to control muscle force) however, the abbreviation "MC" will be used throughout. With the control of muscle force being expressed at the level of the MU (Keen et al., 1994), via the age-related reduction in MUNE and increase in MUP size through MU remodelling (Piasecki et al., 2016*a*), levels of MC seemingly become reduced with ageing through various mechanisms, with older adults displaying varying strategies allowing completion of tasks involving levels of MC (Tracy & Enoka, 2002), such as utilising different muscle activation strategies when stepping down (Hortobagyi & DeVita, 1999).

During muscle contraction, the desired force output fluctuates around an average value rather being a constant level (Enoka et al., 2003). Subsequently, this variability during muscle contraction can be assessed in absolute (standard deviation; SD) or relative terms (coefficient of variation; CoV) to quantify levels of MC via calculating force steadiness (FS); the ability to maintain a submaximal force level around a steady state value (Beck et al., 2011). Typically, the lower the SD and/or CoV, the greater level of FS (thus better muscle force control) which is thought to be beneficial with respect to maintenance of muscle force capacity (Oomen & van Dieen, 2017). As force production requires rapid MU recruitment, fast MU force twitches and high MU discharge rates (Dideriksen et al., 2019), differences in MU activity likely contribute to variation in force fluctuations observed during varying contraction intensities and/or the type of muscle contraction (Enoka et al., 2003).

1.5.1. Current evidence of motor control: the influence of age, exercise interventions and disparity between limbs

FS as a means for assessing MC, often assessed through using horizontal target lines at a set value, has been examined in both the upper and lower limbs (see Keogh et al., (2019) and Oomen & van Dieen, (2017) for reviews). Previous research in the upper limbs has seemingly been focussed in small muscles, such as the first dorsal interosseous (FDI) (Keen et al., 1994; Kavanagh et al., 2016), which are important for dexterity and become affected by the age-related development of tremor, which affects 4% of people over 40 years, increasing up to 14% in people over 65 years of age (Kavanagh et al., 2016). Comparatively, previous evidence surrounding FS in the lower limb is more relevant to ambulation and balance, thus potentially relevant to understanding increased

levels of falls and subsequent fractures evident with ageing (Carville et al., 2007). Importantly, the literature seems to suggest that older adults tend to present with greater force fluctuations (so lower FS) during submaximal contractions compared to young adults (Enoka et al., 2003). Furthermore, it seems that at the lower compared to higher contraction intensities, greater levels of force variation become evident (Enoka et al., 2003). For instance, Galganski et al., highlighted that the difference in FDI FS was greater between old and young adults at 2.5% of maximal voluntary contraction (MVC) force (old: 11.0 ± 1.8%; young: 6.6 ± 0.5%) compared with 50% MVC target force (old: 3.9 ± 0.2%; young: 2.9 ± 0.2%) (Galganski et al., 1993). Interestingly, through interventions, such as resistance exercise training (RET), FS seems improve in older adults (as detailed below and reviewed by Keogh et al., (2019) and Oomen & van Dieen, (2017)), although results are inconclusive between different muscle groups. Therefore, it is important to understand variations in MC, in both the upper and lower limb muscle groups, with age and how intervention strategies may aid improvements in muscle control; thus, likely improving an individual's independence and quality of life.

1.5.1.1. Motor control in the upper limb

Keen and colleagues investigated alterations in finger-abduction force of FDI following 12 weeks of strength training (3 x per week, 6 sets of 10 repetitions at 80% 1-repetition maximum (1-RM)) in both young and older adults (Keen et al., 1994). Pre-training, only young and older females displayed differences in MVC force, however, following 12 weeks of training, both the young and older subjects increased in strength by 36.9 ± 11.9% and 41.2 ± 8.2% respectively (Keen et al., 1994). Furthermore, the authors reported older adults displayed

greater force fluctuations compared to their young counterparts at 2.5, 5 and 20 but not 50% MVC when holding a 20 second isometric muscle contraction (Keen et al., 1994). Post-training, CoV of FS significantly reduced within the older individuals at 2.5 (-29.3 ± 10.2%), 5 (-20.6 ± 10.3%), and 20% (-11.7 ± 14.0%) MVC target forces, with minimal benefits observed in the young (Keen et al., 1994). In a study of 8 weeks basic movement strength training (3 days per week, 5 – 7 sets of 15 repetitions at 30% 1-RM) in older adults, Kobayashi et al., reported the CoV of FS in the elbow flexors (EF) to significantly decline at 10, 30 and 65% MVC in the experimental group but with no changes in the control group (Kobayashi et al., 2014). These differences were attributed to improved muscle coordination due to the type of training performed, although no changes in EMG amplitude were evident in agonist muscles (Kobayashi et al., 2014).

The effects of RET also seem to be evident for improving levels of coordination and tremor in older adults. For example, Kavanagh and colleagues investigated a 6-week (2 x per week, 4 sets, first set at 40-50% 1-RM with last 3 sets using loads only able to be lifted for 8-10 repetitions) RET programme (including bicep curls, wrist flexion and wrist extension exercises) in 10 older adults (>60 years) who had an essential tremor (ET) diagnosis of >1 year. The authors noted an improvement in CoV of finger abduction force at 10 and 60% MVC, with improvements in both the more (both 10 and 60% MVC) and less (60% MVC only) affected limb (Kavanagh et al., 2016). With respect to muscle coordination, Carroll et al., conducted RET targeting the index finger extensor muscles on the performance of a sensorimotor coordination task, consisting of synchronous flexion and extension movements to an auditory pacing signal

(Carroll et al., 2001). Following training, the performance of this task was reported to improve with the finger extensors being recruited in a more consistent fashion; specifically, variability in timing, amplitude and duration of muscle activity were all reduced (Carroll et al., 2001).

1.5.1.2. Motor control in the lower limb

When looking at the lower limb, Beck and colleagues investigated the effects of 8 weeks RET (3 x per week, 3 sets of 10 – 12 repetitions at ~80% 1-RM) in young healthy untrained individuals on levels of FS of the KE and common drive (a term which suggests active motor units are controlled as a pool rather than individually by the central nervous system; De Luca et al., 1982) (Beck et al., 2011). They found that although MVC force increased following RET, levels of common drive and FS remained unchanged (Beck et al., 2011). In the lower leg, Dewhurst et al., investigated differences in isometric contractions of the dorsiflexors (DF) at 5, 10 and 15% MVC in 26 young (23.6 ± 3.4 years) and older (68.6 ± 5.7 years) women (Dewhurst et al., 2007). CoV of force was found to be significantly greater in old compared to younger participants at all contraction levels, with the greatest difference seen at 5% MVC (Dewhurst et al., 2007). Conversely, work from Tracy reported no differences in the dorsiflexion CoV of force between young and older adults, however, they did report differences in the CoV of plantar flexor (PF) force (Tracy, 2007). PF strength was significantly lower (-38%) in older compared to younger adults, with the CoV of force elevated at 2.5 and 5% MVC in older adults (Tracy, 2007). Surprisingly, PF CoV of force was greater in younger individuals compared to old at 30% MVC, with similar values displayed at 10, 50 and 80% MVC (Tracy, 2007). Although not discussed in the work of Tracy et al., the greater CoV of

force in the young participants at 30% MVC may be due to a higher proportion of type II muscle fibres in young compared to older adults, which are more susceptible to fatigue (Allen et al., 2008). Interestingly, Tracy et al., highlight a positive correlation between EF and KE muscles with respect to 1-RM and CoV of force at 5, 10 and 30% MVC (but not 2.5% MVC) (Tracy et al., 2007). This positive correlation was attributed to the EF and KE muscle groups having similar neuromuscular characteristics due to the amplitude of force fluctuations being shown to be inversely related to the number of MUs in the muscle (Hamilton et al., 2004); which is supported by no such correlation being evident between EF or KE with FDI (Tracy et al., 2007).

Discrepancies in levels of FS between young and older adults seemingly become apparent when comparing differing muscle contractions (isometric *vs.* anisometric), as evidenced by Carville and colleagues (Carville et al., 2007). In this study, the authors investigated these two differing contraction states within the quadriceps muscles of 44 young individuals and 78 older adults (34 presenting with a history of falling; Carville et al., 2007). During isometric contractions, older adults with a history of falling presented with a higher CoV of force values in both (stronger/weaker, more/less steady) legs, therefore, showing impaired steadiness compared to older non-fallers and younger subjects (Carville et al., 2007). Further to this, during the anisometric (concentric/eccentric) contractions, older adults (whole group) were significantly less steady than the young group, with eccentric contractions distinguishing differences between the two older sub-groups, with fallers being less steady by 31% (Carville et al., 2007).

1.5.1.3. Alternative methods of improving motor control

It is recognised that not all older adults can perform high-intensity and demanding exercise such as RET, often due to physical limitations (Barry & Carson, 2004). With this in mind, Christou and colleagues examined 20 weeks of Taiji training on levels of MC in 16 older adults (Christou et al., 2003). The authors found that the training elicited an increase in MVC of ~20% (+19.5 ± 4.9%), in addition to reduced CoV of FS of a similar magnitude (-18.9 ± 3.3%; grouped value across 2, 30, 60 and 90% MVC) (Christou et al., 2003). Further to this, Zech and colleagues performed a systematic review focussing on the use of balance training on neuromuscular control. Although this review only included studies conducted in younger individuals, improvements in EMG activity (determined by calculating root mean square, EMG mean amplitude voltage and/or EMG median frequency) and PF rate of force development (RFD) were reported after balance training, with these changes not observed in the associated control groups (Zech et al., 2010). These changes were primarily postulated to be associated with neural adaptations rather than alterations to muscle properties, with potential positive alterations to feedback of mechanoreceptors leading to potential central nervous system reorganisation in terms of sensorimotor integration and therefore alterations to motor response (Zech et al., 2010). Taken together, alterative training methods such as those stated above, may lead to beneficial improvements in MC; although more conclusive evidence needs to be sought to address the intensity/frequency at which beneficial effects are seen, and in which specific groups improvements are possible.

1.6. Physiological mechanisms for improving motor control

The age-related decline in MU number (Tomlinson & Irving, 1977; Lexell et al., 1983; Piasecki et al., 2016*a*) and subsequent MU remodelling (Piasecki et al., 2016*a,* 2016*b,* 2018*a*), undoubtedly suggests that the level of MC produced by the muscle is affected with advancing age, although direct evidence for this is lacking. Despite this, there are several physiological mechanisms, both from a central and peripheral origin, which aid explanation of the reduced MC seen in older adults, and also in the improvements observed with exercise training.

Strength gains observed during the first few weeks of RET are commonly attributed to neural adaptations, such as MU recruitment, MU firing rate (FR) and reduced coactivation of antagonist muscles (Beck et al., 2011), therefore improving the "communication" within the neuromuscular system. Due to the force exerted by a muscle during a voluntary contraction being dependent on the number of MUs recruited and the rates at which they discharge APs (Enoka & Duchateau, 2017), it is possible that such alterations may also be partly responsible in affecting levels of FS during submaximal muscle contractions (Beck et al., 2011). A resultant factor of age-related MU remodelling (Piasecki et al., 2016*a*) is that larger MUs are activated earlier at a lower force level and FR (Oomen & van Dieen, 2017), subsequently displaying greater fluctuations in MU force and discharge rates (Enoka et al., 2003). Importantly, differences in FS seem to depend more on MU discharge characteristics than force capacity of active MUs across differing tasks and individuals (Enoka & Duchateau, 2017). Furthermore, the irregularity of MU FR in older compared to young muscle is

likely to contribute to the heightened CoV of FS and thus reduced muscle control (Enoka et al., 2003). Interestingly, greater irregularity of MU FR is exhibited during eccentric compared to concentric contractions in older adults (Enoka et al., 2003), which is likely able to explain differences in FS during anisometric contractions, especially between older "fallers" and "non-fallers" (Carville et al., 2007). Importantly, following RET it is suggested there is an increased tendency of MUs to fire synchronously in trained compared to untrained individuals (Carroll et al., 2001), which could lead to improved FS. Subsequently, the use of interventions to improve FS, either through RET or other means (e.g. balance/physical exercise involved high levels of coordination) may have beneficial effects on improving the synchronous nature of MU FR, thus improving force fluctuations in older adults.

Importantly, it cannot be dismissed that central mechanisms may also contribute to the age-related decline in muscle control. Increased MU discharge variability has been suggested to implicate force variability with age (Enoka et al., 2003). Cross-correlation between force variability and MU FR has been shown to occur where MU discharge rate is largest (Oomen & van Dieen, 2017), with the variability being suggested to be caused by common drive of the central nervous system (De Luca et al., 1982). Conversely, MU discharge rate (i.e. consecutive firings of MUPs) has been suggested to have a larger effect on force control variability than the loss of MUs (Enoka et al., 2003), although other studies have shown no changes in discharge rate despite evidence of force variability (Galganski et al., 1993; Dewhurst et al., 2007); thus providing an unclear answer as to the role of central mechanisms on MU discharge rate (Oomen & van Dieen,

2017). Further evidence of the potential influence from central mechanisms has come from Dettmers and colleagues who reported that as force increases during isometric contractions, neural activity increases in the primary motor cortex and caudal supplementary motor area (Dettmers et al., 1996). It has been proposed that the potential for interference between functionally proximal areas of the cerebral cortex increases with the degree to which they are activated (Carroll et al., 2001). Therefore, an increased neural spread of activation increases the potential for the activation of neural elements which would lead to interference with optimal task performance (Carroll et al., 2001), and could subsequently impact the recruitment of MUs leading to ineffective movement control. Following exercise training (specifically RET), if each MU within a muscle is capable of producing greater force, fewer MUs would need to be recruited to produce the movement outcome (Carroll et al., 2001). Hence, a reduction in cortical activation and subsequent reduction in neural interference would be present, consequently leading to improved MC (Carroll et al., 2001). With respect to neural changes of spinal origin, particularly due to skill training, conditioning both the spinal stretch reflex (SSR) and H-reflex (a measure of spinal alpha motoneuron excitability and an electrical analogue of the SSR) (Adkins et al., 2006) may impact an individual's MC. A decrease in the H-reflex is thought to occur due to an increase in motoneuron firing threshold and an increase due to reduced inhibition of the motoneuron, thus operant conditioned training may induce alterations to the H-reflex (and SSR) which could lead to better movement corrections (Adkins et al., 2006).

Finally, fluctuations in force output could be caused by the coactivation of the antagonist muscle by either differences in the average level of coactivation and/or alternating agonist/antagonist muscle activation (Enoka et al., 2003). For example, older adults coactivate antagonist muscles more frequently and at greater intensities compared to younger individuals when exerting an abduction force using the index finger (Enoka et al., 2003). Such differences in muscle antagonist coactivation have also been observed in larger muscle groups, with Tracy and Enoka highlighting greater levels of coactivation between biceps femoris (antagonist) and VL, vastus medialis (VM) and rectus femoris (RF; agonists) when conducting isometric and anisometric KE contractions (Tracy & Enoka, 2002). Subsequently, it is unsurprising that increased levels of antagonist coactivation and/or the sporadic pattern of this coactivation has been proposed to alter levels of FS during isometric contractions (Enoka et al., 2003), although this is not a consistent finding in the literature (Oomen & van Dieen, 2017).

1.7. Aims and purpose of the current study

As synthesised above, the current literature suggests that there are potential positive effects of exercise training-based interventions, such as RET, for improving levels of FS, which suggests improved MC in older adults. However, evidence for this along with understanding of the underlying physiological mechanisms driving these adaptions is, to date, inconclusive. It must also be considered that not all individuals, specifically older adults, may be able to conduct such "traditional" (e.g. RET) exercise interventions. Therefore, the aim of the current study was to investigate the effect of a novel 4-week exercise training strategy (coined motor control training (MCT) which aimed to target/train force control), in both VL and TA, on MC (specifically the control

of muscle force) and MU parameters. The training period of 4 weeks was based on evidence (see section 2.5. for more detail) that neuromuscular alterations to training occur ~2 – 4 weeks after training commences and before morphological adaptations (Keogh et al., 2019). *In vivo* measurements at the single MU level, conducted in the present study, allow for the exploration of adaptations following MCT at the smallest component of the human neuromuscular system; hence, providing novel insight to the contribution of alterations to MU parameters (e.g. MU FR and MUP size) with respect to MC. The present study was originally designed to include an age comparison of the effects of our MCT regime on young and older adults. However, due to the impact of the COVID-19 pandemic this was not possible. Therefore, the current study includes data from young volunteers only. Based on evidence from the current literature, it was hypothesised that in our young volunteers, 4 weeks of MCT would not elicit changes in MVC force, but would improve FS and a measure of complex force tracking (CFT) in both of the trained muscles, and increased synchrony of MU discharge times, through reduced FR variability, would occur following MCT.

2. Methodology

2.1. Ethical approval

The current study was approved by the University of Nottingham Faculty of Medicine and Health Sciences Research Ethics Committee (Reference Number: C16122016) and was conducted in accordance with the Declaration of Helsinki. Participants were recruited from a University staff and student population. Potential participants contacted a member of the research team via email or telephone to receive more information on what the study entailed prior to organising an initial screening visit (see below). All participants were provided with written information (via a participant information sheet (PIS); Appendix 1.1.) about the details of the study, at least 48 hours before providing written informed consent (healthy volunteer consent form; Appendix 1.2.) to participate, after having had the opportunity to ask a member of the research team any questions.

2.2. Participant characteristics

Six healthy participants (4 females, 2 males; Table 2.1.) completed the study. Prior to enrolment, all participants were deemed healthy via an initial screening visit where written informed consent was obtained prior to a routine blood sample being taken to assess health parameters (e.g. liver and kidney function), in addition to conduction of an electrocardiogram, and a discussion about the participants medical history. Additionally, habitual physical activity levels were assessed by the self-administered International Physical Activity Questionnaire (IPAQ) prior to participating in the study. Participants were excluded from the current study if they presented with; a body mass index (BMI) <18 or >35 $kg \bullet m^{-}$

[2] and/or any significant musculoskeletal disorders. Additionally, participants were withdrawn from the study if they were unable to complete 10 out of 12 MCT sessions. Individuals were asked to maintain their habitual levels of physical activity throughout the duration of the study to enable us to assess the effects of the addition of MCT. The testing phase lasted 4 weeks which included a baseline and follow-up experimental visit, in addition to 12 fully supervised MCT sessions (3 x per week for 4 weeks; see Figure 2.1. and detailed below).

Table 2.1. *Participant characteristics. Muscle anthropometric data is for the right leg only. Data are presented as mean ± SD.*

		Whole group (*n* = 6; 4 F, 2 M)
	Age (years)	25.2 ± 6.8
	Height (cm)	167.7 ± 7.4
	Weight (kg)	63.3 ± 13.4
	BMI ($kg \cdot m^{-2}$)	22.5 ± 4.0
Vastus Lateralis	CSA (cm^2)	20.1 ± 7.3
	MT (cm)	2.4 ± 0.6
	L_f (cm)	7.6 ± 0.6
	PA (°)	21.1 ± 3.4
Tibialis Anterior	CSA (cm^2)	6.6 ± 1.6
	MT (cm)	2.6 ± 0.4
	L_f (cm)	7.1 ± 0.9
	PA (°)	10.4 ± 2.4

BMI, body mass index; CSA, cross-sectional area; F, females; L_f, fascicle length; M, males; MT, muscle thickness; PA, pennation angle.

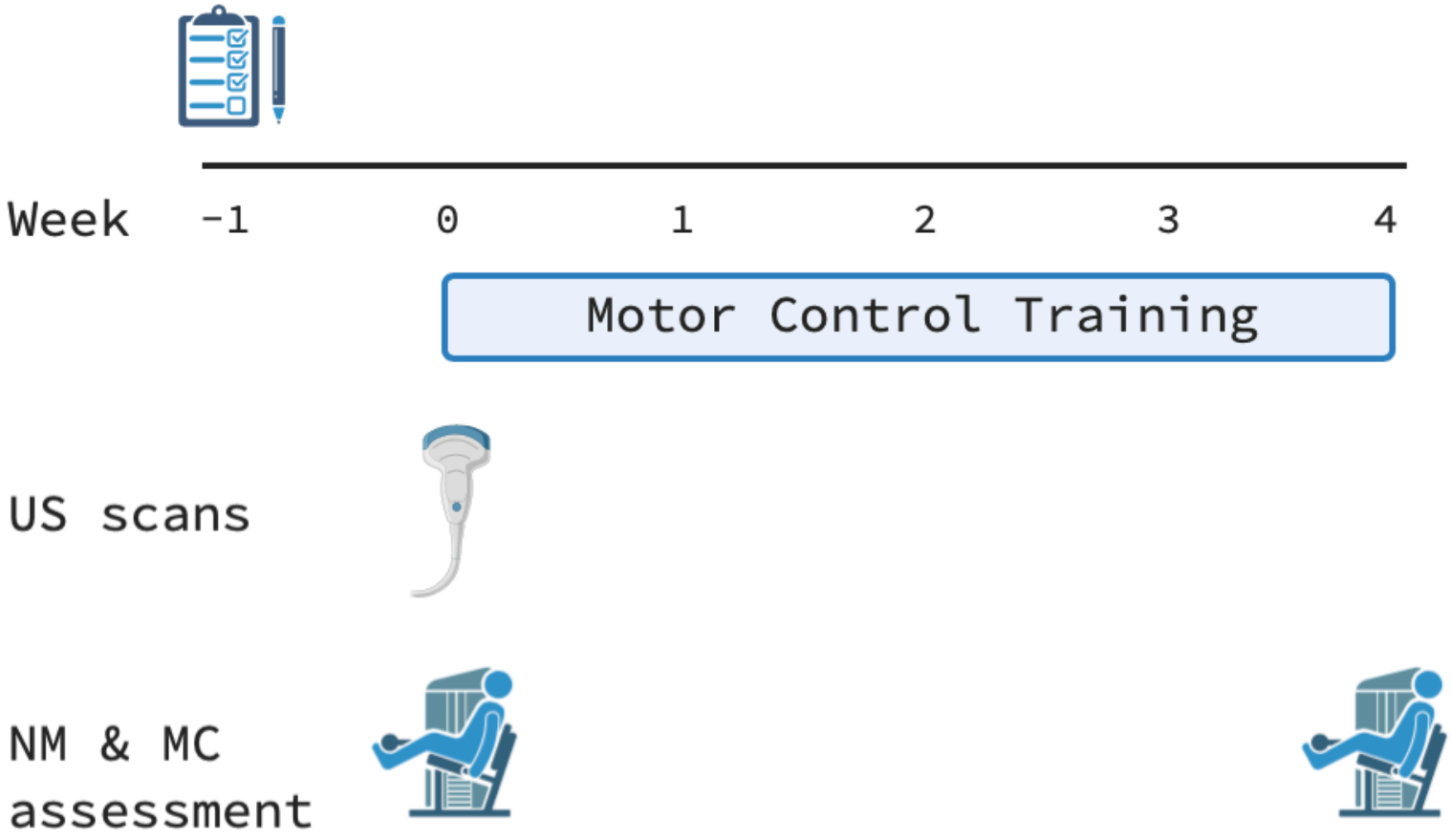


Figure 2.1. *Schematic representation of experimental protocol. A screening visit preceded all experimental testing visits. Baseline and follow-up testing followed the same procedures with ultrasound (US) scans to assess muscle cross-sectional area (CSA) and architecture, occurring prior to neuromuscular (NM) and motor control (MC) assessments. Four weeks of motor control training then ensued prior to the follow-up testing visit, which occurred ~48 hours after the last training session.*

2.3. Neuromuscular assessment

Neuromuscular assessment, specifically involving iEMG, followed methodologies outlined by Piasecki and colleagues (Piasecki et al., 2018*a*). Data was acquired from the VL and TA muscles in both the right (trained) and left (untrained) leg for both baseline and follow-up visits. Both sEMG and iEMG (used to identify alterations at a MU level) were used to assess muscle electrophysiological alterations to MCT.

2.3.1. Identification of motor point

Initially, the motor point of each muscle was identified as the site of the muscle that produces the largest visible twitch using a low stimulation current (Piasecki et al., 2016*b*). To determine motor point location, electrical stimulation (Digitimer DS7AH, Digitimer, Welwyn Garden City, Hertfordshire, UK) was delivered on the skin, over the muscle, using a cathode probe (Medserve, Daventry, UK). The stimulator was set to a compliance voltage of 400 vs with a 50 μs pulse width. Typically, VL has a distal motor point around 90 mm from the knee joint, with the proximal motor point located around 220 mm from the lateral femoral condyle; and TA has a motor point around 120 mm from the tibial head (Piasecki et al., 2018*b*).

2.3.2. Electromyography recordings

After identification of the motor point, the skin around the area of motor point location was shaved and cleaned using an alcohol swab. A sEMG electrode (Disposable self-adhering AG-AGCL electrodes, 95 mm^2, Ambu Neuroline, Baltorpbakken, Ballerup, Denmark) was then placed directly over the motor

point, with a reference electrode placed on the patella tendon and a grounding electrode placed on the patella. Intramuscular EMG (iEMG) recordings were obtained using disposable concentric needle electrodes with a recording area of 0.07 mm^2 (Model N53153: Teca, Hawthorne, NY). Both sEMG and iEMG signals were sampled at 10 KHz and 50 KHz respectively. Two CED 1902 amplifiers (Cambridge Electronics Design Ltd, Cambridge, UK) band-pass filtered sEMG and iEMG signals at 5 Hz to 5 KHz and 10 Hz to 10 KHz respectively. Signals were digitised with a CED Micro 1401 data acquisition unit (Cambridge Electronic Design Ltd, Cambridge, UK). All sEMG, iEMG and force signals were recorded and displayed in real-time via Spike2 software (CED, Cambridge, UK, version 9). Data were analysed offline in Spike2 (version 9) software. To ensure electrode placement was kept similar between pre- and post-MCT visits, the positioning of all electrodes was measured from anatomical landmarks and recorded.

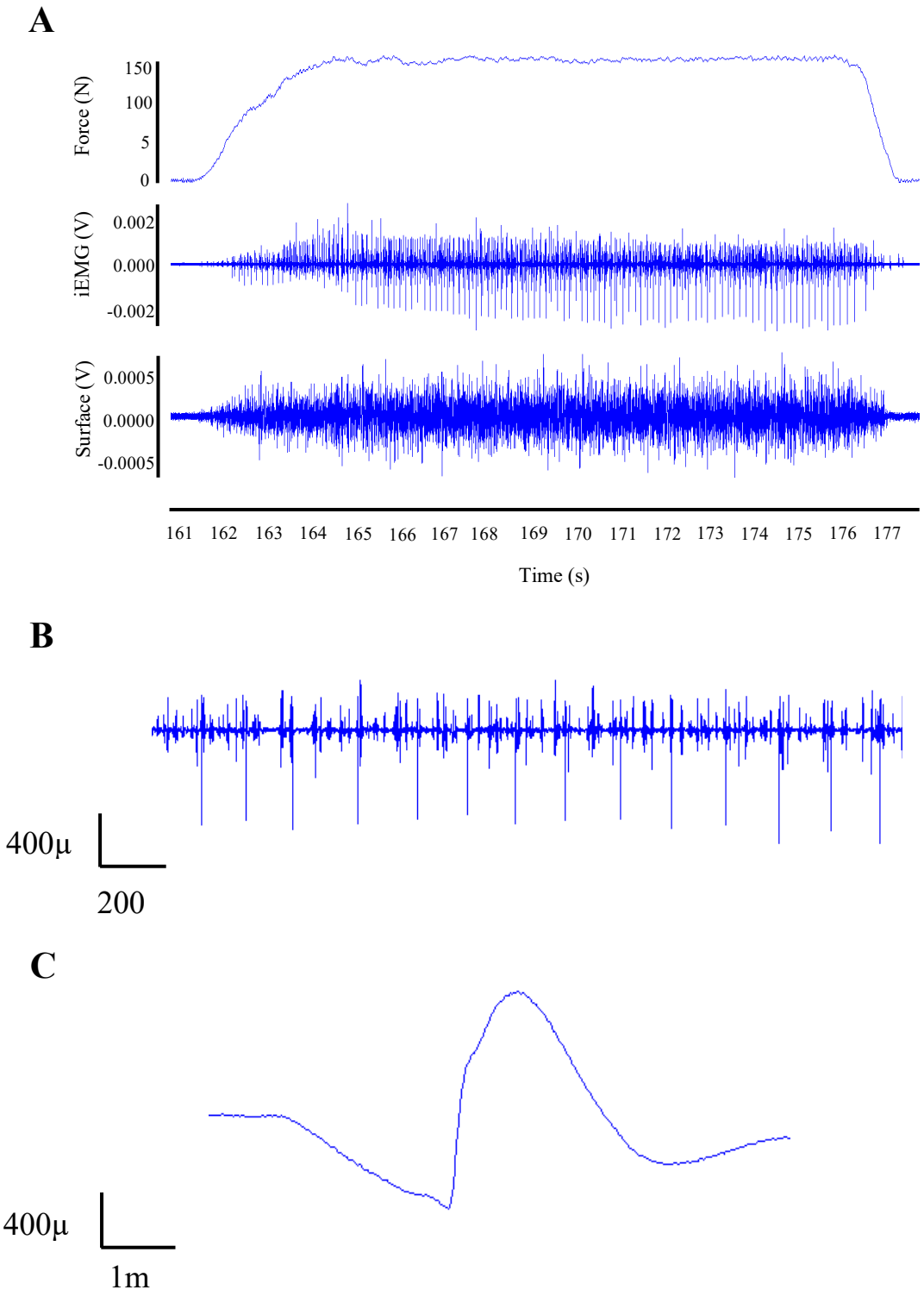


Figure 2.2. *Typical raw data collected showing motor unit potentials (MUPs) recorded by intramuscular EMG (iEMG) during a sustained isometric muscle contraction at 25% MVC.* ***A:*** *force (top), iEMG (middle) and surface EMG (sEMG; bottom) traces during a sustained isometric contraction lasting ~15 seconds.* ***B:*** *iEMG data shown with a reduced time window to highlight more detail of MUPs.* ***C:*** *a single MUP isolated from the trace shown in B.*

2.4. Experimental procedures

Participants arrived at the laboratory for experimental testing days at ~09.00 a.m. (± 1 hour) having undergone an overnight fast (>10 hours), with post-MCT testing occurring ~48 hours after the last training session. Initially, ultrasound scans (US) of the VL and TA of the right leg were performed to allow for anthropometrical assessment. All scans were conducted in accordance with previous literature (Franchi et al., 2014, 2018) to assess muscle cross-sectional area (CSA) and thickness, in addition to muscle architecture (fascicle length and pennation angle). For assessment of VL, the researcher measured the midpoint of the line from the greater trochanter to the midpoint of the patella. The lateral and medial borders of VL were distinguished using the ultrasound probe in a vertical orientation, with the borders and midpoint of the muscle being marked on the skin. For TA, scans occurred at 30% of the distance from the midpoint of the patella to the lateral malleolus, with the borders being distinguished in a similar way to VL. Muscle CSA was assessed using extended field of view methodology, with single measures taken at different points of the muscle (see Franchi et al., (2018) for a more detailed overview). All data collected via ultrasound was acquired as an image, allowing offline analysis via ImageJ software (Laboratory of Optical and Communication, University of Wisconsin-Madison, WI, USA). US took ~30 minutes in total.

Participants next sat in a purpose-built dynamometer with hips and knees flexed at ~90º for VL assessment with each leg being secured to a force transducer (Piasecki et al., 2016*c*) just above the malleoli. For TA assessment, the knee and ankle were flexed at ~90º in a seated position, with a non-compliant strap

securing the mid-foot to a force transducer. After a standardised warm-up of each exercise (~10 sustained contractions held for ~5-10 seconds, ranging from ~10-70% MVC), participants were instructed to perform MVCs of KE and DF. MVCs lasted ~3 seconds and attempts were separated by ~60 seconds, with real-time visual feedback and strong verbal encouragement provided. The highest peak force (N) was determined as maximal force. Each MVC was repeated 3 times, with further attempts required if >10% variation was observed (Piasecki et al., 2016*b*).

Participants were then asked to relax their muscles to enable insertion of the needle electrode (iEMG) at ~60-80° to the skin, ensuring the tip of the needle was beneath the sEMG electrode (motor point) for both VL (Figure 2.3.) and TA (Figure 2.4.) in the trained and untrained legs. Participants then performed a series of voluntary contractions (simple force tracking tasks) at 10, 25 and 40% of their MVC lasting 12 – 15 seconds with ~15 seconds separating each contraction. Following each set of contractions, the needle was withdrawn ~5-10 mm and the bevel rotated 180°, for a total of 4 – 6 contractions in spatially distinct areas.

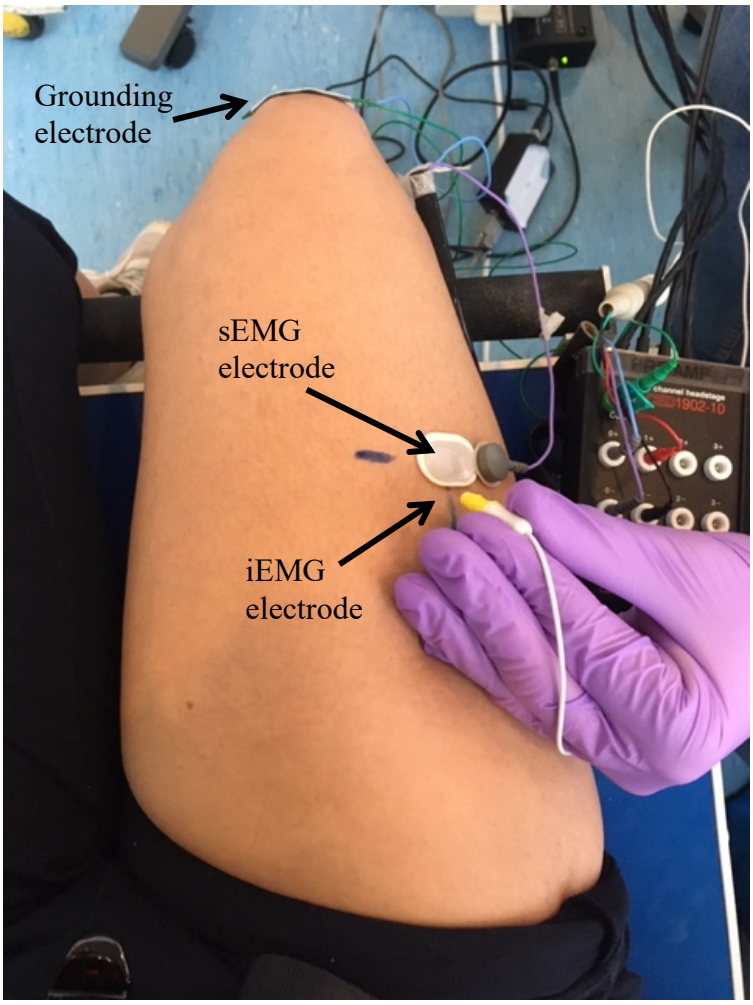


Figure 2.3. *Photographic image of data collection set-up using iEMG for the VL muscle. The participants ankle was secured via a non-compliant strap just above the malleoli to a force transducer, with the hips and knees flexed at ~90º. A reference electrode (out of image) was placed on the patella tendon with a grounding electrode positioned on the patella. The sEMG electrode was positioned over the motor point, with the needle (iEMG) electrode inserted into the muscle at ~60-80° to the skin, ensuring the tip of the needle was beneath the sEMG electrode.*

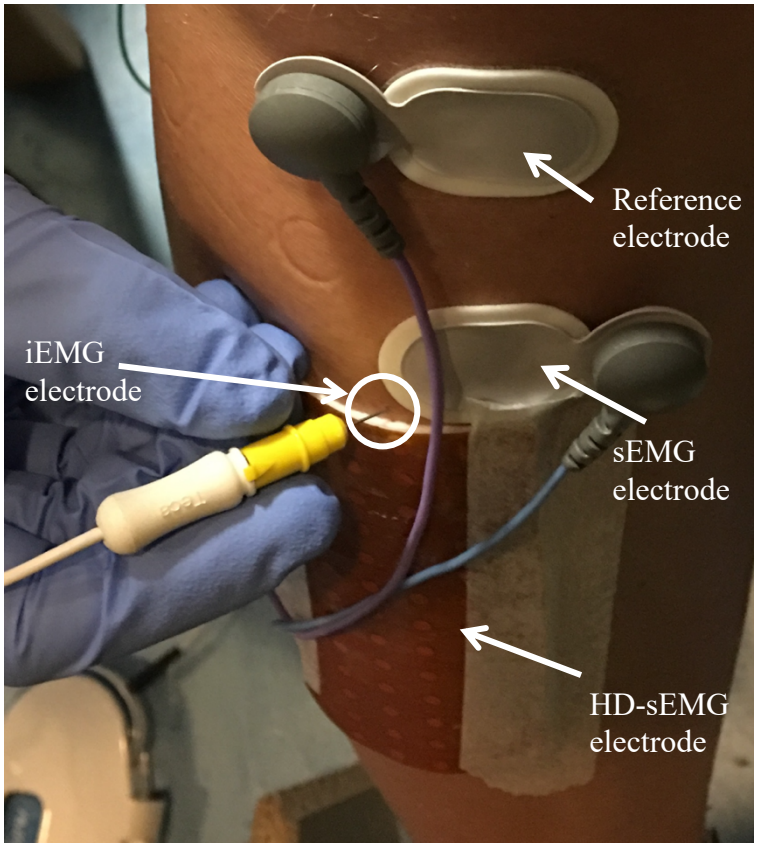


Figure 2.4. *Photographic image of data collection set-up using iEMG in the TA muscle. In a seated position, the participants mid-foot was secured to a transducer via a non-compliant strap, with the knee and ankle flexed at ~90º. A reference electrode placed on the patella tendon with a grounding electrode (out of image) positioned on the patella. The sEMG electrode was positioned over the muscle, with the needle (iEMG) electrode inserted into the muscle at ~60-80° to the skin, ensuring the tip of the needle was beneath the sEMG electrode. Additionally, in this image, a high-density sEMG (HD-sEMG) electrode (containing 64 monopolar electrodes) was positioned over the muscle to obtain additional data (not included in this thesis).*

Participants next completed a series of CFT tasks (created using OT Bioelettronica software, Torino, Italy) in a randomised order, at 10, 25 and 40% MVC to assess levels of MC. A familiarisation contraction was performed at 25% MVC prior to the assessment contractions being recorded. Contractions consisted of a number of oscillations (8) at a set amplitude (± 4%) lasting for 30

seconds at 10 and 25% MVC and 20 seconds for 40% MVC contractions, with 10-second ramps each side to allow force to steadily increase and decrease to and from the desired contraction intensity (see Figure 2.5.). Contractions were exported and analysed in Spike2 (Version 9) software, where a virtual channel was created (subtracting the performed path from the requested path) and the area under the curve (AUC, N*s) of this channel was representative of the level of deviation from the target line, reflecting MC (muscle force control) ability.

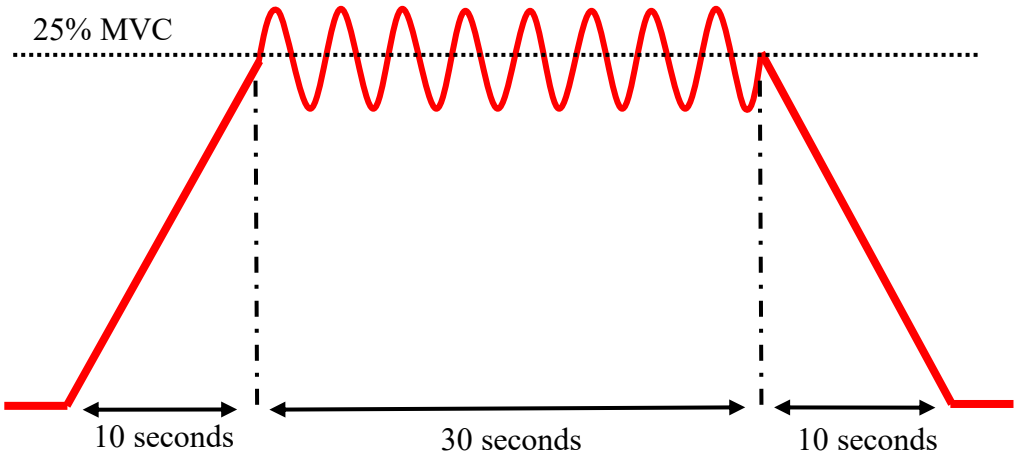


Figure 2.5. *Diagrammatic representation of CFT task at 25% MVC, adapted directly from OT Bioelettronica software.*

Finally, participants completed a battery of physical function tests to assess balance and power before and after MCT. All balance tests conducted on the trained and untrained leg with eyes open and closed, were assessed using a Footscan plate (Footscan, 200 Hz, RSscan International, Belgium) allowing measurement of centre of pressure, and the displacement of this, during static one-legged standing. For balance assessment with eyes open, participants were asked to focus on a fixed point in front of them and keep their focus for the

duration of the test (30 seconds). A 5-second countdown was given before instructions to lift their leg, 2 seconds before the recording period began (with participants closing their eyes 1-second before recording began for eyes closed assessment). Distance travelled (mm), the displacement of centre of pressure, was recorded and taken for further analysis through applying the following function, thus ensuring both the test time and distance travelled were accounted for, where *t* is the time the test lasted (s), and *d* is distance travelled (mm), to calculate a balance index score (AU):

$$= (31-t)*(0.01*(1.002^{(31-t)}))*d$$

Counter-movement jumps (CMJ; G-walk, BTS Bioengineering, USA) were used to assess power (kW), with jump height (cm) and take-off speed ($m.s^{-1}$) values also obtained. The G-Walk device was positioned by the researcher at the S1 vertebrae. Participants were instructed to stand neutrally with their hands on their waist and to bend down as far as 90° before jumping up in one fluid movement. Participants were allowed 2 practice jumps before recording started, with 3 jumps being conducted for both pre- and post-MCT measures. The jump which elicited the greatest power was taken for further analysis.

2.5. Motor control training

All participants were required to perform fully supervised MCT for 4 weeks, with 3 sessions each week. Our main rationale for exploring the novel exercise training programme of MCT, was based on our aim of eventually transferring this training modality into older adults. Furthermore, the MCT may be relevant to periods of prehabilitation to limit muscle functional decline post-surgery, due

to the length of the training period lasting 4 weeks; the typical length of prehabilitation prior to surgery (Durrand et al., 2019). Previous literature has utilised RET (i.e. ~80% 1 rep max (Schulze et al., 2002; Oates et al., 2010)) or balance training (Zech et al., 2010) in order to improve force steadiness predominantly in older adults; a measure typically quantified to assess muscle control (Beck et al., 2011). However, such training may not be feasible in a number of older adults, due to the relatively high intensity demands of RET that are required to elicit change (Kobayashi et al., 2014). In addition, older adults have been reported to have reduced proprioception and coordination (Goble et al., 2009), meaning balance training may also prove difficult. The use of MCT would, therefore, be less demanding for older participants and potentially lead to substantial improvements or maintenance in muscle control; hence influencing functional movement capacity (Carville et al., 2007). With respect to RET, it is well accepted within the literature that neural mechanisms (e.g. MU synchronisation, muscle excitability, central motor drive) are predominantly responsible for early strength gains (Campbell et al., 2019), typically observed within the first few weeks of training (Del Balso & Cafarelli, 2007; DeFreitas et al., 2011). Due to our focus on neuromuscular adaptations, rather than hypertrophic/muscle structural changes through training, we, therefore, selected 4 weeks for the training duration as neuromuscular responses should be evident within this time frame.

The MCT itself consisted of 6 complex force tracking tasks of the KE and DF for each training session. Only the right leg was trained, with the left leg acting as a control limb. Participants completed 2 contractions at 10, 25 and 40% of

baseline MVC (6 contractions in total) in a randomised order. The number of oscillations (either 6, 8 or 10) and amplitude (either ±2%, ±4% or ±8%) of the sinusoidal waves of the complex tracking tasks varied to that used in experimental testing (set number oscillations and amplitude as stated above) and was again randomised for each MCT session. Contractions lasted 20 – 30 seconds depending on contraction intensity and were separated by ~60 seconds rest.

2.6. Decomposition-enhanced spike triggered averaging electromyography analysis

Procedures for identifying, recording and analysing individual MUPs and calculating near fibre (NF) parameters were conducted in accordance with (Piasecki et al., 2016*c*) and have been described in detail elsewhere (Stashuk, 1999*b*; Boe et al., 2004). In brief, decomposition-based quantitative electromyography (DQEMG) software was used to analyse both iEMG and sEMG signals (Piasecki et al., 2016*c*). Visual inspection of all MUPs and surface MUPs (sMUPs) occurred to ensure the sMUP corresponded with the MUP. Markers corresponded to the onset of the MUP and sMUP, onset of negative phase (sMUP only), the end of the MUP and sMUP, and positive/negative peaks of waveforms; and were adjusted where appropriate where markers were not correctly positioned by the analysis software.

2.6.1. Motor unit potentials

Individual MUPs (Figure 2.6.) were identified, utilising the iEMG signal from MU potential trains (MUPT) of separate MUs. MUPTs composed of MUPs from

more than one MU were excluded, with those having fewer than 40 MUPs being carefully inspected as whether to be included in analysis. MUP amplitude was measured from the maximal positive and negative peaks and the area was taken as the total area within the MUP duration (onset to end).

2.6.2. Surface motor unit potentials

Corresponding sMUPs were automatically identified for each MUP. Visual inspection occurred to reject any sMUPs if the onset did not occur within 10 ms of the MUP. Individual MUPs were used to "trigger" the corresponding sMUP recorded by the sEMG. The sMUPs were then aligned and ensemble-averaged to estimate an overall mean sMUP. The mean sMUP was taken as representative of the "size" of the average MU recorded during the contraction at 10, 25 and 40% MVC.

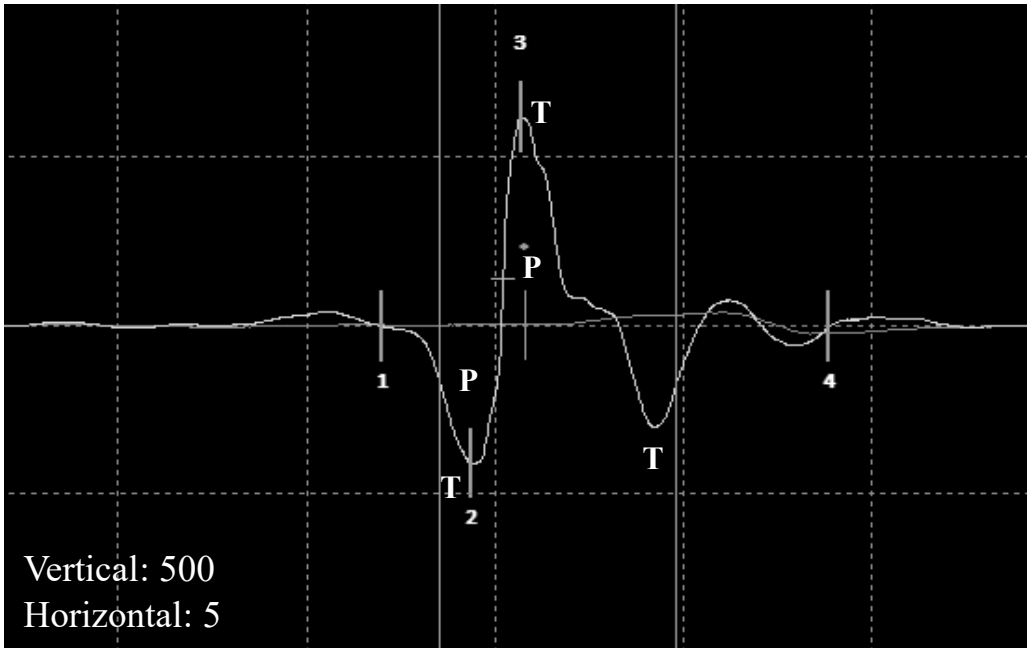


Figure 2.6. *Example image of intramuscular EMG measurements from the VL at 25% MVC. Motor unit potential (MUP) is averaged from 83 observations of the same MUP. Numerical markers indicate: 1, start of MUP; 2, positive peak amplitude; 3, negative peak amplitude; 4, end of MUP. P, indicates a phase (defined as the number of components above or below the baseline) of the MUP; T, indicates a turn (defined as a change in direction of the waveform of at least 25 μV) of the MUP.*

2.6.3. Motor unit discharge rates, complexity and neuromuscular junction stability

Individual MUPs were further used to assess MU discharge rates, complexity and NMJ transmission stability. For discharge rate analysis, the MUPs within a MUPT were identified and expressed as a function of recording time (s^{-1} or Hz). The complexity of MUs was assessed from the number of phases and turns of the template MUPs. The number of "phases" of the template MUP was defined as the number of components above or below the baseline (Piasecki et al., 2016*c*). A "turn" was defined as a change in direction of the waveform of at least 25 μV (Piasecki et al., 2016*c*).

A NF MUP (Figure 2.7.) was taken as the acceleration of a MUP identified by applying a second-order, low-pass differentiator to the MUP. This essentially reduced the recording area of the needle electrode to within 350 μm; thus, ensuring only the closest fibres significantly contribute to the NF MUP. As a result, this reduced artefacts and interference from active distant fibres outside of this recording area (Stashuk, 1999*b*). The NF fibre count, a measure of fibre density, was obtained from the template NF MUP. NF jiggle was expressed as a percentage of total template NF MUP area, allowing measurement of the variability of consecutive NF MUP.

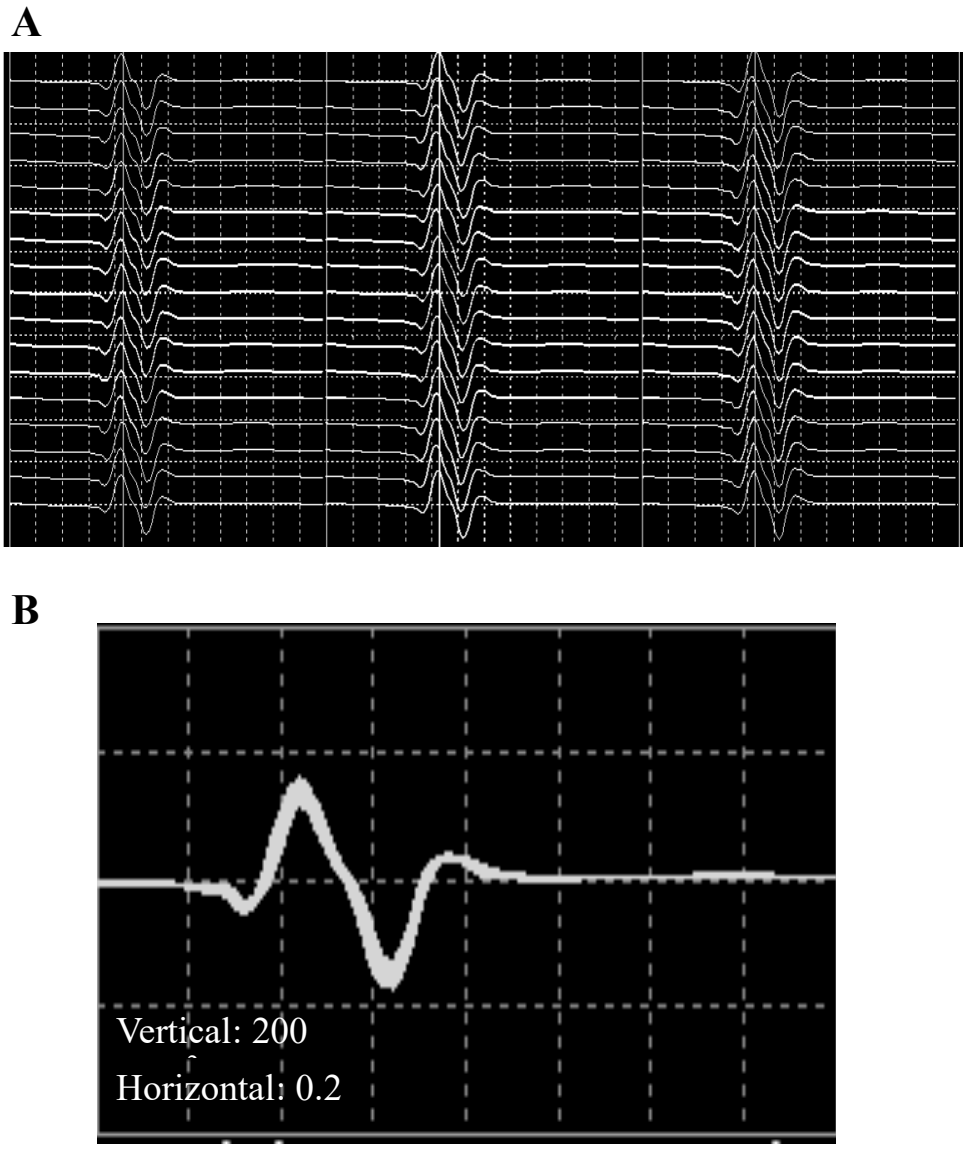


Figure 2.7. *Example images of a single near fibre (NF) motor unit potential (MUP) from decomposed intramuscular EMG recordings from the VL at 25% MVC.* ***(A)*** *raster plot of a NF motor unit potential train (MUPT) showing 51 consecutive firings from the same motor unit (MU).* ***(B)*** *shimmer plot with the NF MUPs from the MUPT in A overlaid.*

2.7. Statistical Analysis

Data are presented as mean ± standard deviation (SD) unless stated otherwise. Initially, data were analysed using Shapiro-Wilks test for normality to confirm normal distribution of data. Data (MVC force, FS, CFT and balance index scores) were subsequently analysed using a two-way repeated measures ANOVA (condition x time) to assess measures in both the trained and untrained legs pre- and post-MCT. Any significant interaction effects were followed up with appropriate post-hoc tests using Bonferroni correction to identify where significant differences existed. Data for CMJ were analysed using paired Student's t-test pre- and post-MCT. Multi-level mixed effects linear regression models were used to analyse the single MU data (collected via iEMG) with *Leg* and *Timepoint* as factors. Interactions were first examined, and where present individual coefficients for each leg are reported. Where no interactions existed, they were removed from the model and *Leg* and *Timepoint* are reported individually, with a single beta coefficient and 95%CI presented. Adjusted beta values and 95%CI are reported for all parameters. Statistical significance was accepted at $p < 0.05$. Data analysis was performed using both GraphPad Prism Version 8 (GraphPad Software, CA, USA) for analysis involving two-way repeated measures ANOVA and paired Student's t-test, with the MU analysis being conducted in STATA SE Version 16 (StataCorp, Texas, USA).

3. Results

3.1. Maximal voluntary contraction force

There was a significant main effect of condition (trained *vs.* untrained) for KE, but not DF, MVC force ($p = 0.029$) with the trained leg being stronger than the untrained leg at both baseline (mean difference = 37.42 N; $p = 0.013$) and follow-up testing (mean difference = 45.43 N; $p = 0.006$). Following 4 weeks MCT, MVC force was not altered in either the trained or untrained leg for KE (Figure 3.1.; trained, pre = 486 ± 180 N, post = 495 ± 201 N, $p = 0.637$; untrained, pre = 448 ± 171 N, post = 450 ± 173 N, $p > 0.9999$) or DF (Figure 3.2.; trained, pre = 183 ± 66 N, post = 201 ± 83 N, $p = 0.180$; untrained, pre = 169 ± 50 N, post = 190 ± 71 N, $p = 0.112$).

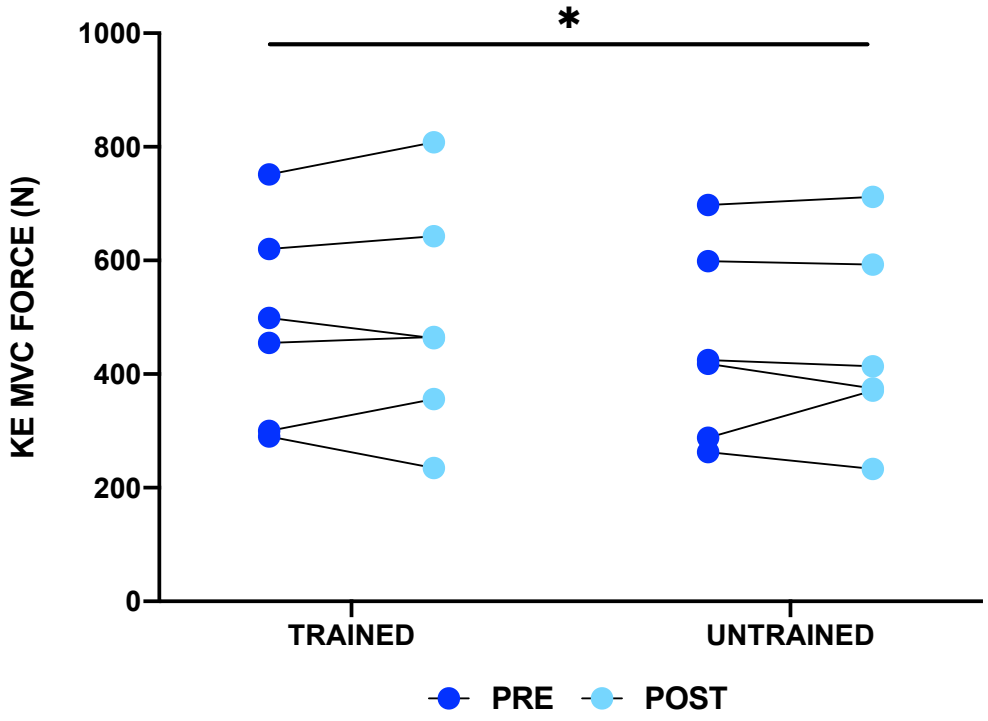


Figure 3.1. *Knee extension (KE) maximum voluntary contraction (MVC) force (N) pre- and post-motor control training (MCT) in the trained and untrained limb. *, $p < 0.05$ (main effect of condition (training)).*

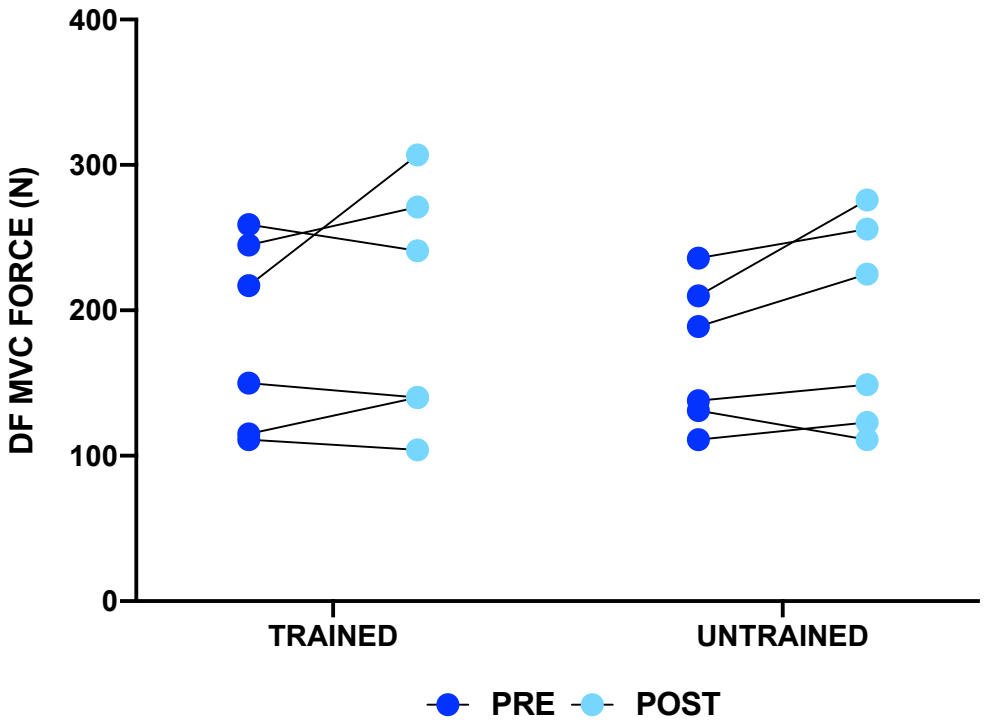


Figure 3.1. *Dorsiflexor (DF) maximal voluntary contraction (MVC) force (N) pre- and post-motor control training (MCT) in the trained and untrained limb.*

3.2. Physical function

Statistical analysis revealed no significant differences (between legs) or changes following MCT in all balance measures and all CMJ parameters (all $p > 0.05$; Figures 3.3. to 3.7.).

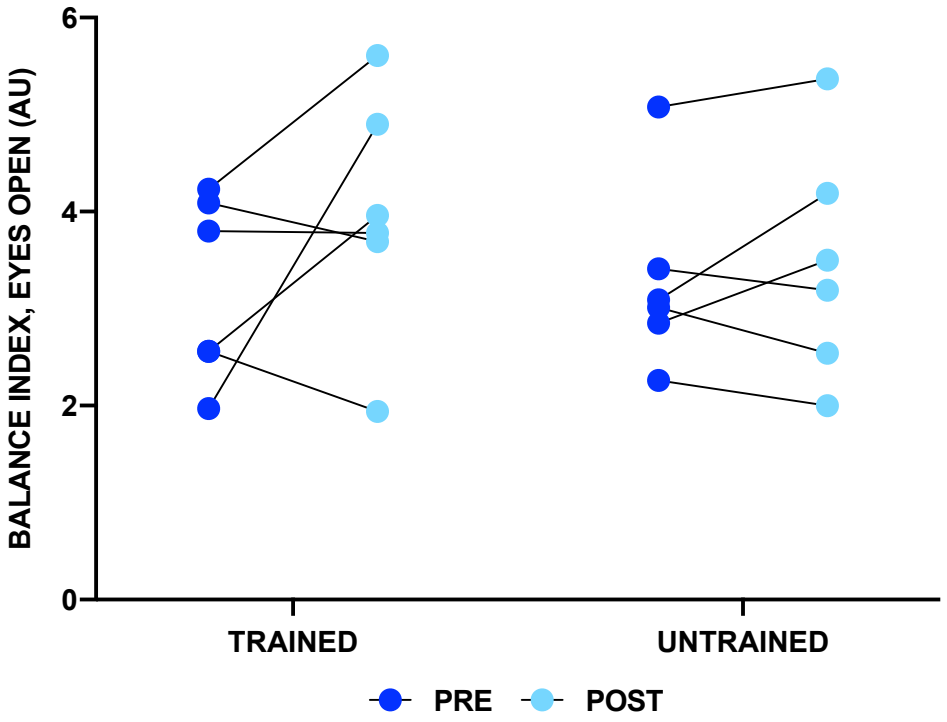


Figure 3.23. *One-legged balance (with eyes open), pre- and post-motor control training (MCT) in the trained and untrained limb.*

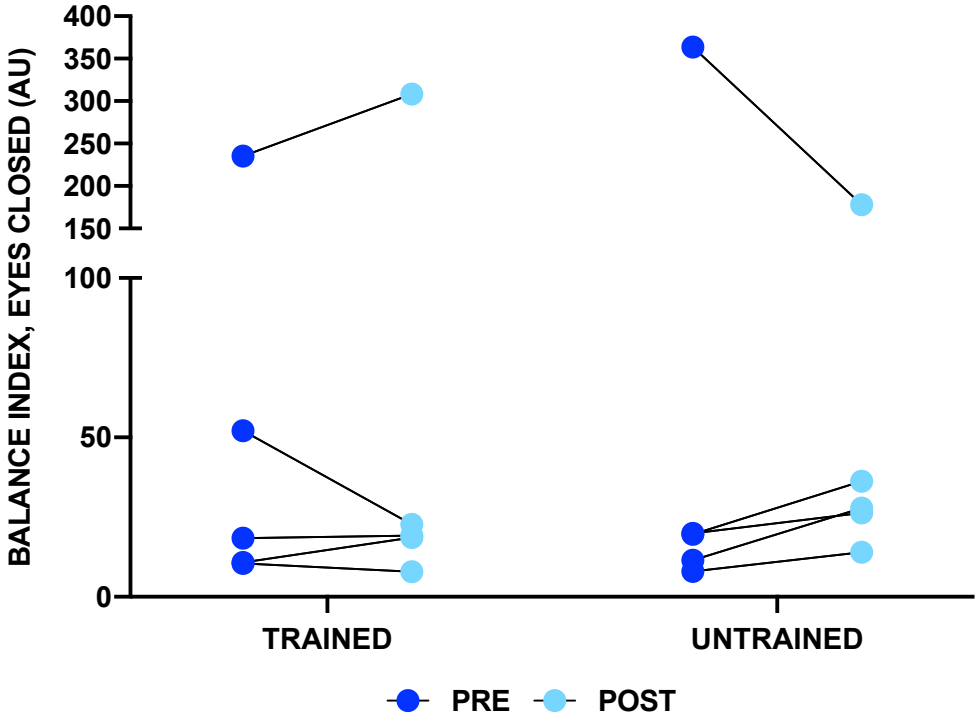


Figure 3.2. *One-legged balance (with eyes closed; n = 5), pre- and post-motor control training (MCT) in the trained and untrained limb.*

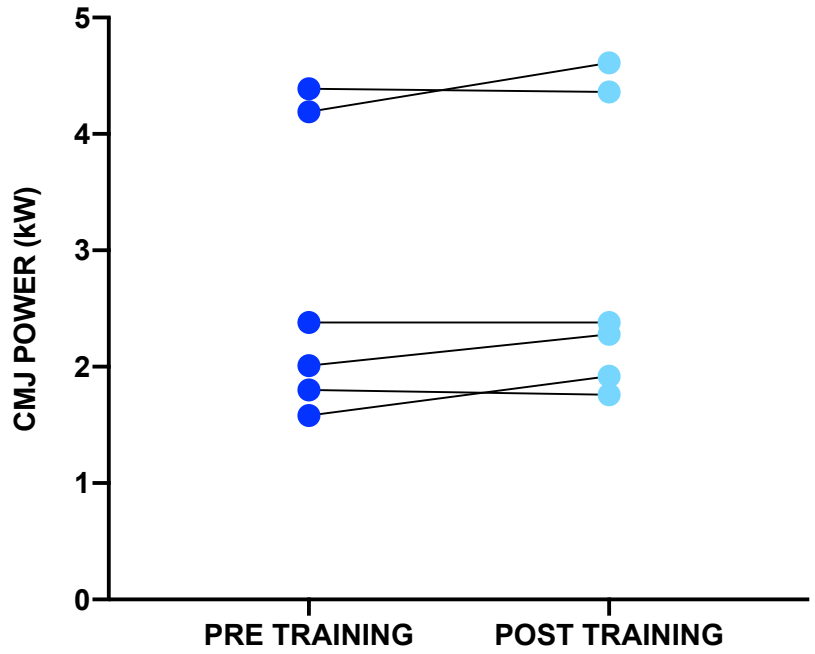


Figure 3.2. *Counter movement jump (CMJ) power (kW) pre- and post-motor control training (MCT).*

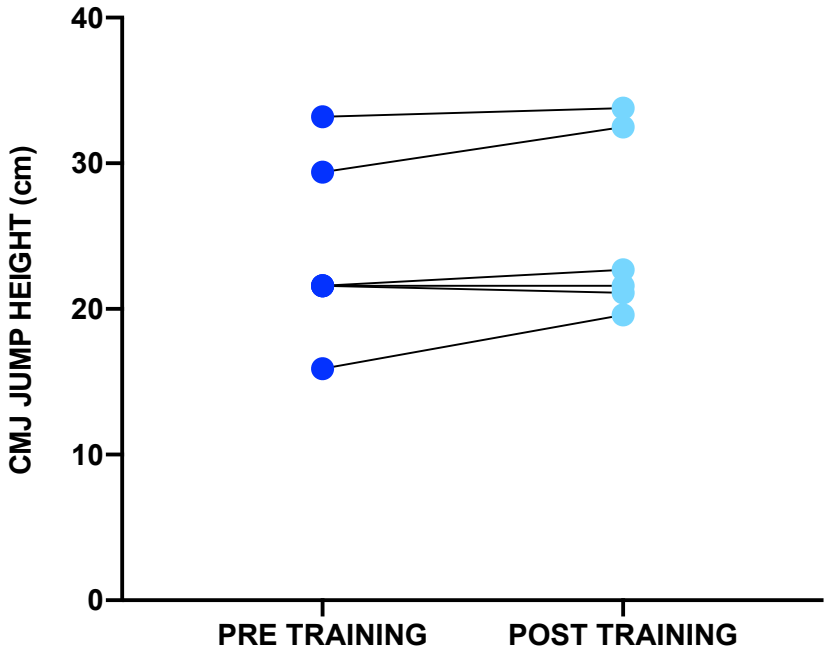


Figure 3.26. *Counter movement jump (CMJ) height (cm) pre- and post-motor control training (MCT).*

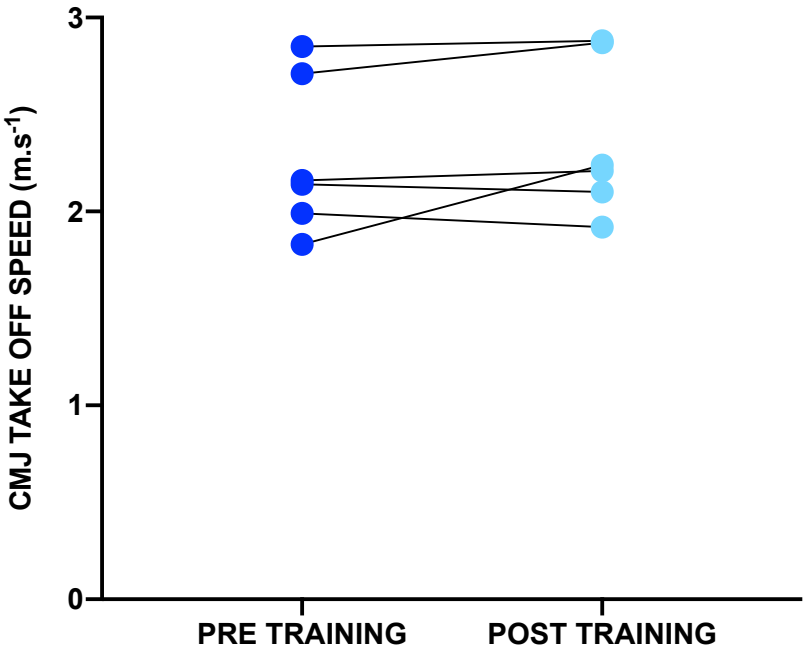


Figure 3.2. *Counter movement jump (CMJ) take off speed (m.s^{-1}) pre- and post-motor control training (MCT).*

3.3. Force steadiness

3.3.1. Knee extensors

A significant main effect of condition was only observed at 25% MVC (Figure 3.9.; $p = 0.024$), with the trained leg being significantly different to the untrained leg at follow-up testing ($p = 0.032$) at 25% MVC. Despite this, MCT led to no improvements in the trained and untrained leg with respect to FS at 10% (Figure 3.8), 25% and 40% MVC (Figure 3.10.).

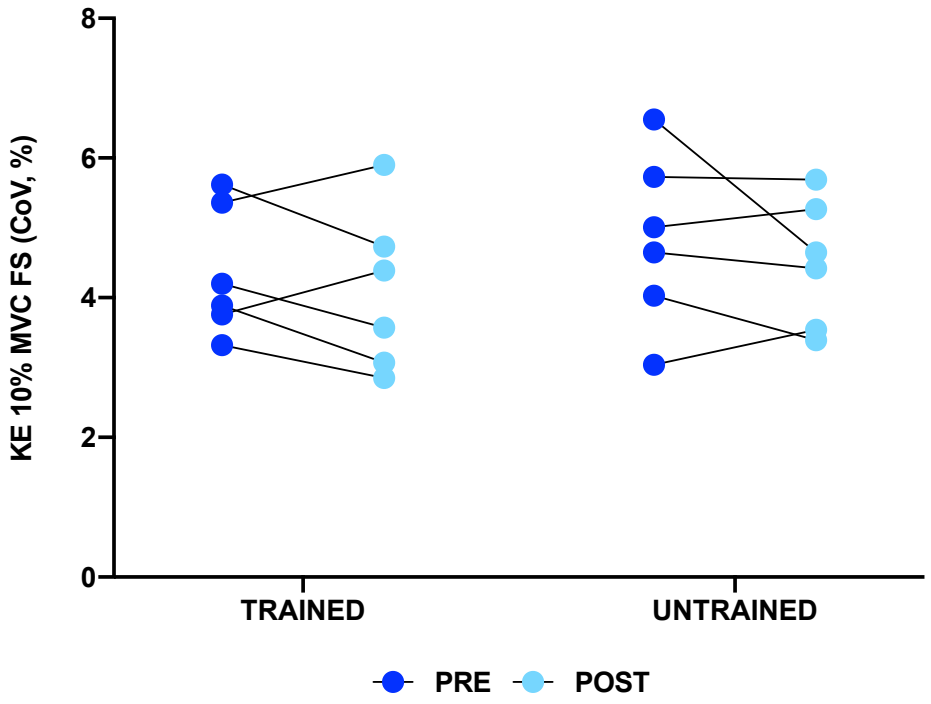


Figure 3.3. *Knee extensor (KE) force steadiness (FS; coefficient of variation, CoV (%)) at 10% maximal voluntary contraction (MVC) pre- and post-motor control training (MCT) in the trained and untrained limbs.*

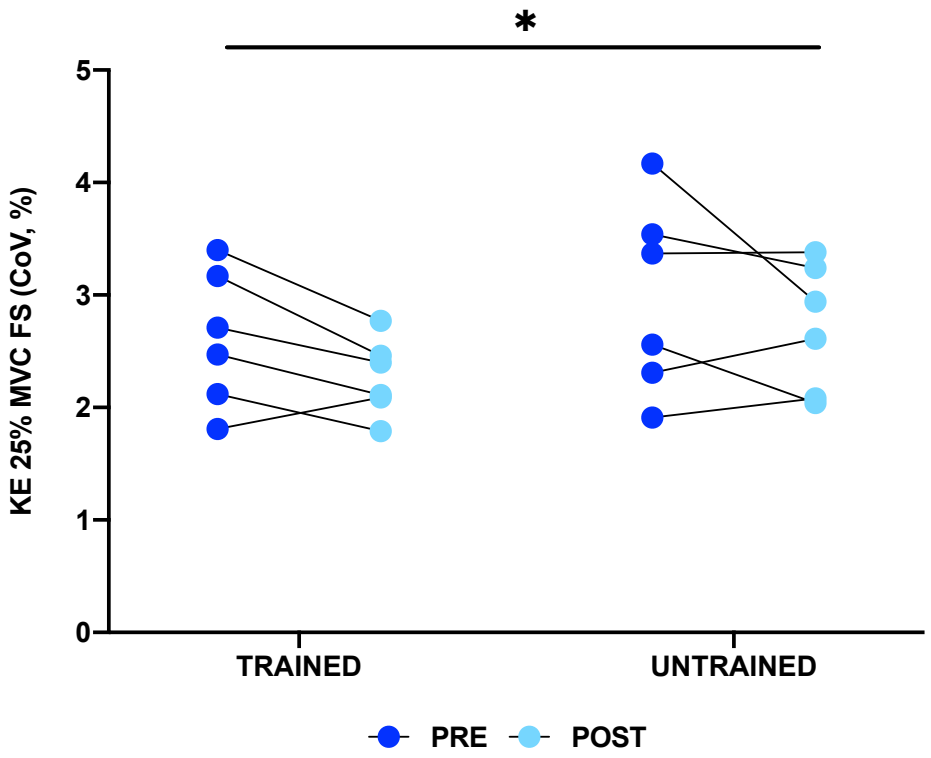


Figure 3.3. *Knee extensor (KE) force steadiness (FS; coefficient of variation, CoV (%)) at 25% maximal voluntary contraction (MVC) pre- and post-motor control training (MCT) in the trained and untrained limbs. *, $p < 0.05$ (main effect of condition (training)).*

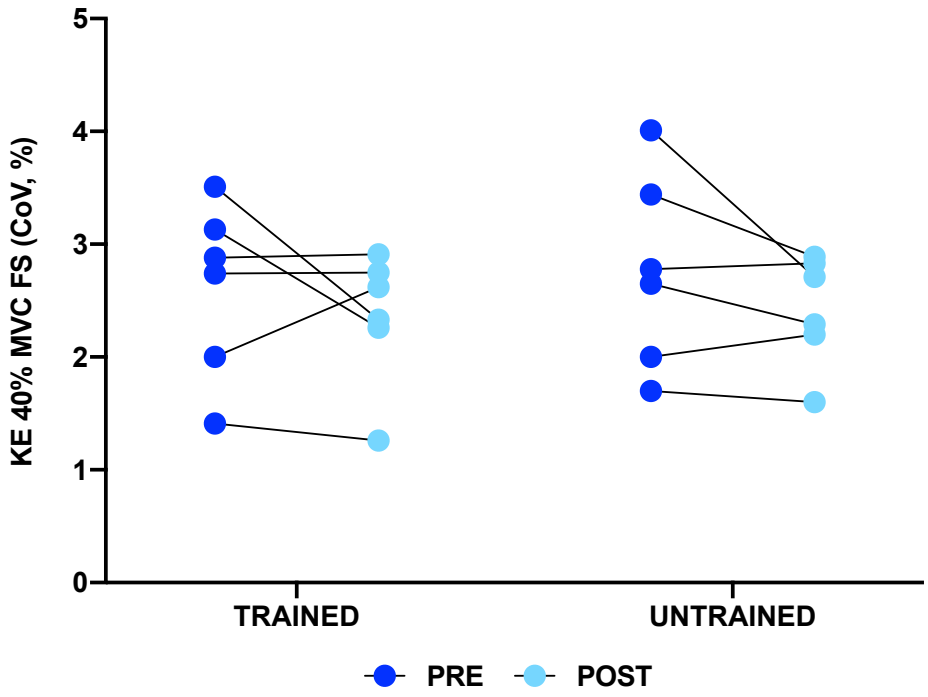


Figure 3.3. *Knee extensor (KE) force steadiness (FS; coefficient of variation, CoV (%)) at 40% maximal voluntary contraction (MVC) pre- and post-motor control training (MCT) in the trained and untrained limbs.*

3.3.2. Dorsiflexors

There were no significant differences in DF FS between the trained and untrained limbs before or after MCT, with no significant difference in the changes observed in each leg at 10% MVC (Figure 3.11.), 25% MVC (Figure 3.12.) or 40% MVC (Figure 3.13.) (all $p > 0.05$).

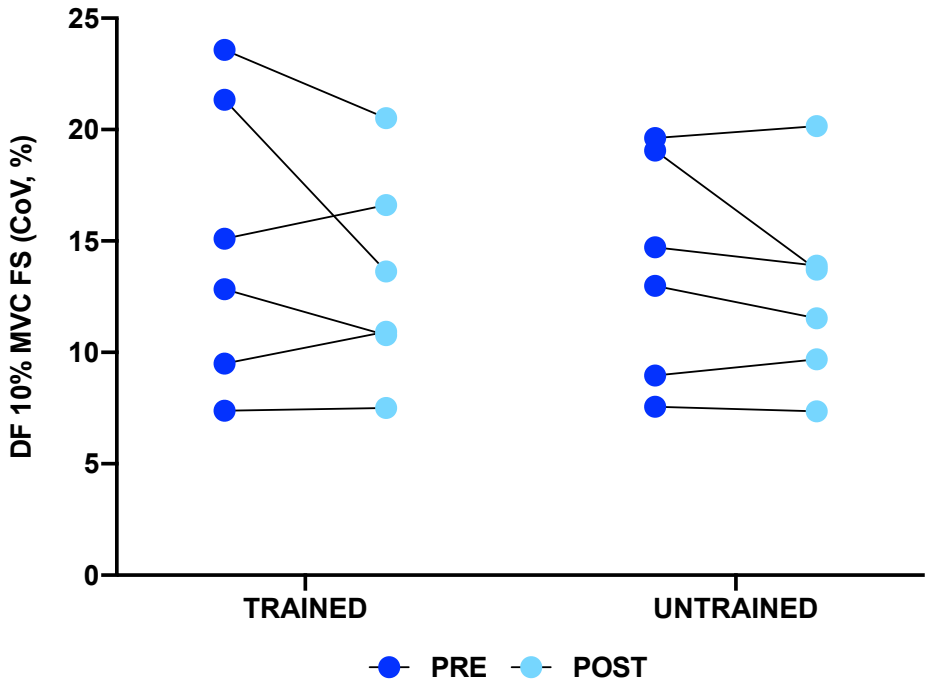


Figure 3.3. *Dorsiflexor (DF) force steadiness (FS; coefficient of variation, CoV (%)) at 10% maximal voluntary contraction (MVC) pre- and post-motor control training (MCT) in the trained and untrained limbs.*

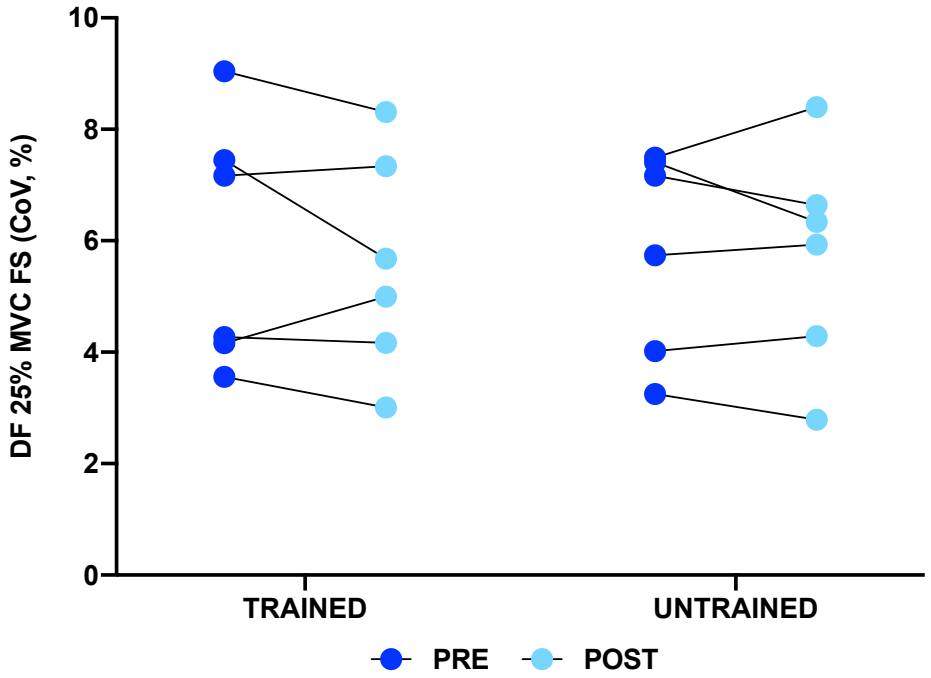


Figure 3.3. *Dorsiflexor (DF) force steadiness (FS; coefficient of variation, CoV (%)) at 25% maximal voluntary contraction (MVC) pre- and post-motor control training (MCT) in the trained and untrained limbs.*

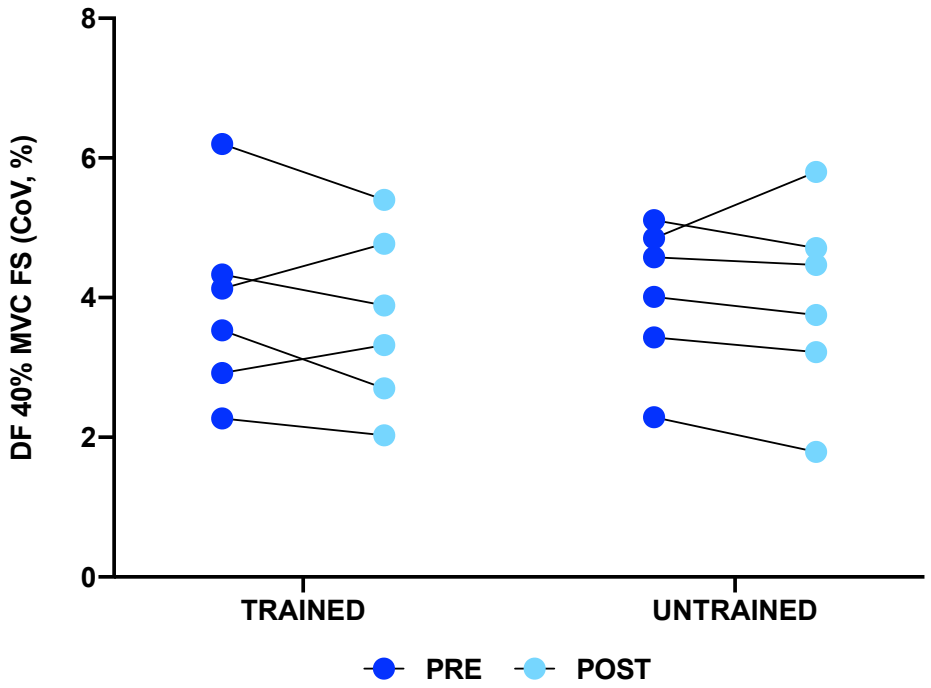


Figure 3.3 *Dorsiflexor (DF) force steadiness (FS; coefficient of variation, CoV (%)) at 40% maximal voluntary contraction (MVC) pre- and post-motor control training (MCT) in the trained and untrained limbs.*

3.4. Complex force tracking

3.4.1. Knee extensors

Following MCT, CFT displayed a significant main effect of time (pre *vs.* post) at 10% MVC (p = 0.004), with weaker significance also achieved at 25% (p = 0.040) and 40% MVC (p = 0.041). A significant interaction effect (condition*time) was also present at 40% MVC (p = 0.037). More specifically, within the trained limb, CFT significantly improved (evidenced through decreased AUC (N*s)) following MCT at 10% MVC (Figure 3.14.; 30.39 ± 4.71 *vs.* 17.93 ± 2.83 N*s, p = 0.0005), 25% MVC (Figure 3.15.; 33.97 ± 9.25 *vs.* 22.94 ± 4.09 N*s, p = 0.015) and 40% MVC (Figure 3.16.; 35.25 ± 5.88 *vs.* 24.34 ± 3.84 N*s, p = 0.0005). CFT also significantly improved in the untrained limb

at 10% (29.15 ± 6.52 *vs.* 21.53 ± 3.32 N*s, $p = 0.005$) and 40% MVC (40%, 34.49 ± 8.01 *vs.* 28.38 ± 4.69 N*s, $p = 0.008$) but not 25% MVC ($p = 0.369$).

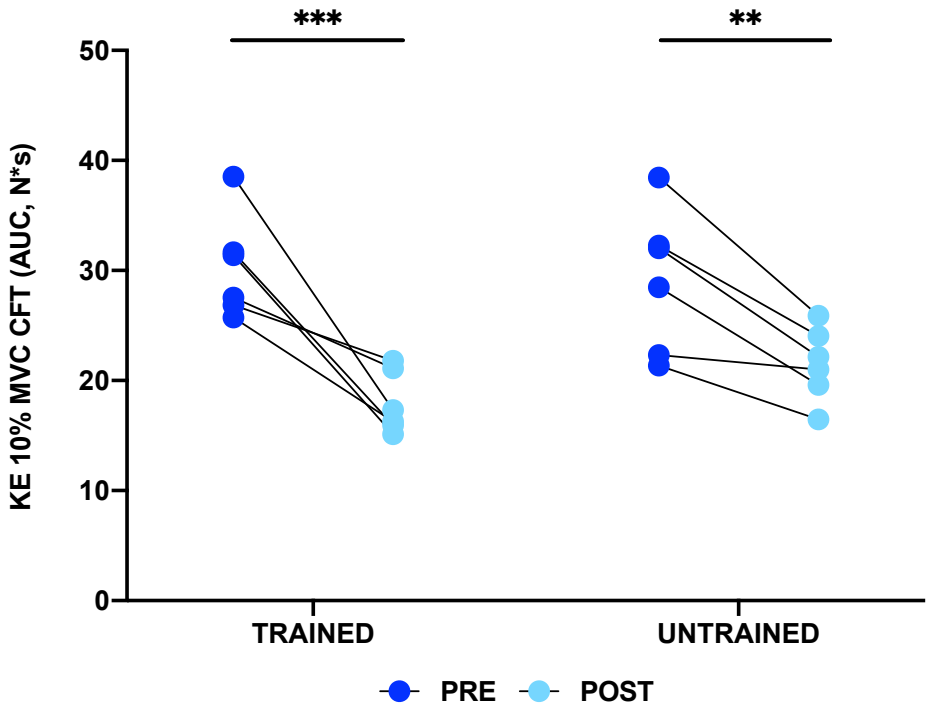


Figure 3.4 *Knee extensor (KE) complex force tracking (CFT; area under the curve, AUC (N*s)) data at 10% maximal voluntary contraction (MVC) pre- and post-motor control training (MCT) in the trained and untrained limb. **, $p < 0.01$; ***, $p < 0.001$.*

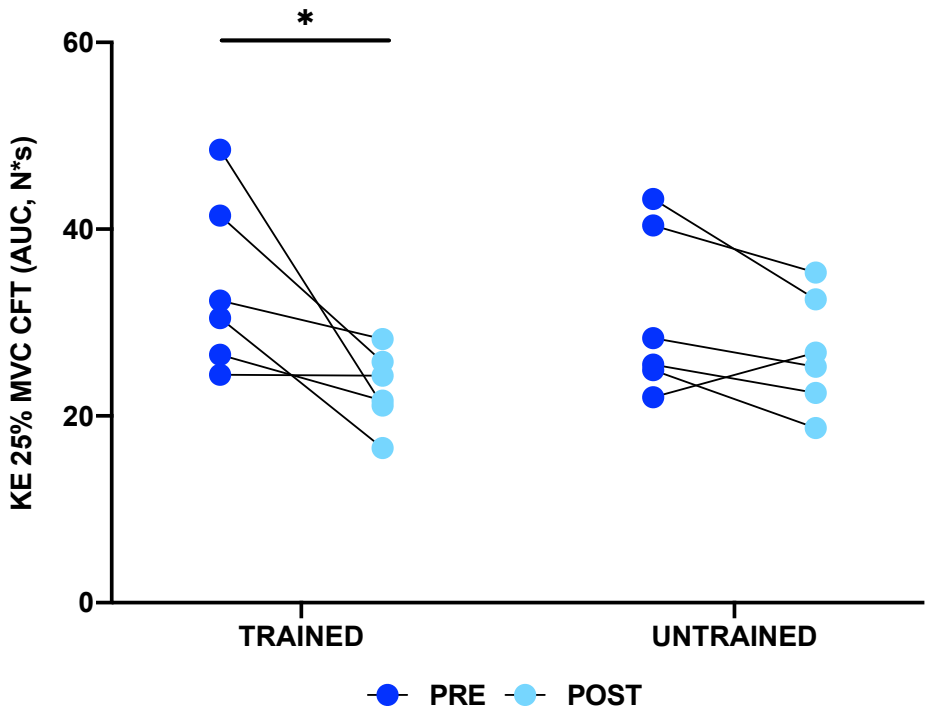


Figure 3.4 *Knee extensor (KE) complex force tracking (CFT; area under the curve, AUC (N*s)) data at 25% maximal voluntary contraction (MVC) pre- and post-motor control training (MCT) in the trained and untrained limb. *, $p < 0.05$.*

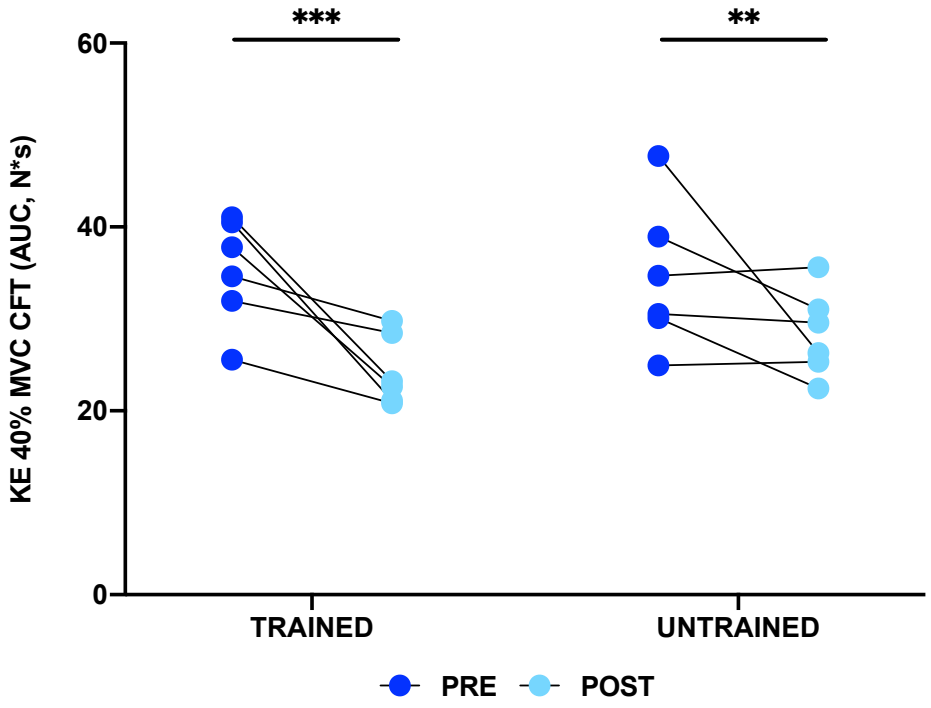


Figure 3.4 *Knee extensor (KE) complex force tracking (CFT; area under the curve, AUC (N*s)) data at 40% maximal voluntary contraction (MVC) pre- and post-motor control training (MCT) in the trained and untrained limb. **, $p < 0.01$; ***, $p < 0.001$.*

3.4.2. Dorsiflexors

Following MCT, a main effect of time (pre *vs.* post) was seen at all (although weaker at 40% MVC) target levels for the DF (10% MVC, $p = 0.031$; 25% MVC, $p = 0.003$; 40% MVC, $p = 0.049$). Specifically, CFT in the trained limb significantly improved at 25% (Figure 3.18.; 40.14 ± 4.59 N*s *vs.* 26.65 ± 3.66 N*s, $p = 0.003$) and 40% MVC (Figure 3.19.; 42.86 ± 11.21 N*s *vs.* 28.13 ± 4.75 N*s, $p = 0.036$). Again, the untrained leg showed a significant improvement in DF CFT but only at 10% MVC (Figure 3.17.; 38.47 ± 9.98 N*s *vs.* 28.11 ± 9.68 N*s, $p = 0.042$).

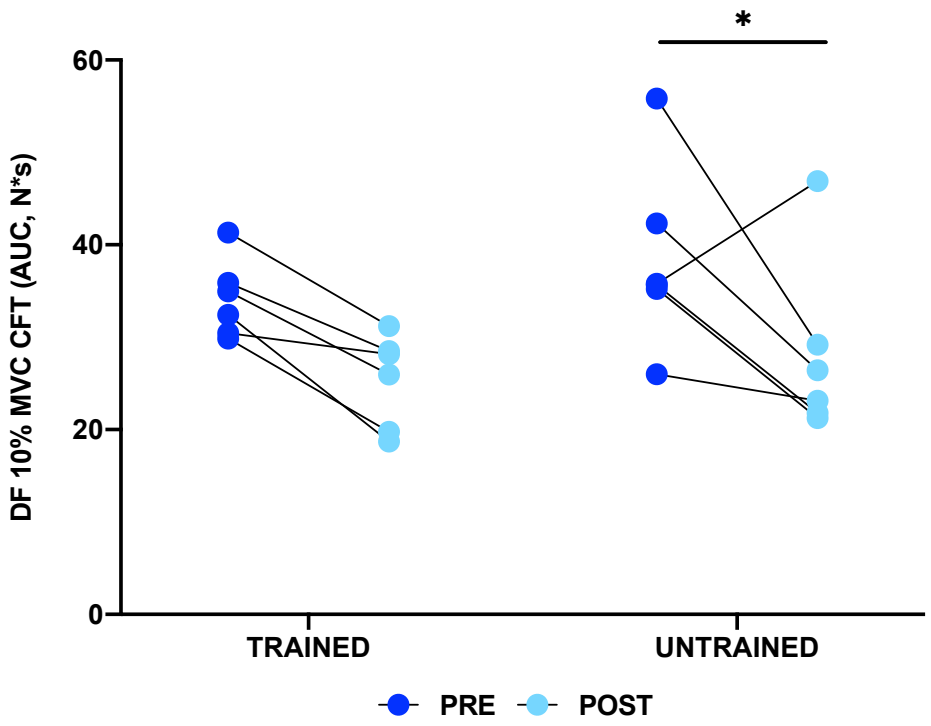


Figure 3.4 *Dorsiflexor (DF) complex force tracking (CFT; area under the curve, AUC (N*s)) data at 10% maximal voluntary contraction (MVC) pre- and post-motor control training (MCT) in the trained and untrained limb. *, $p < 0.05$.*

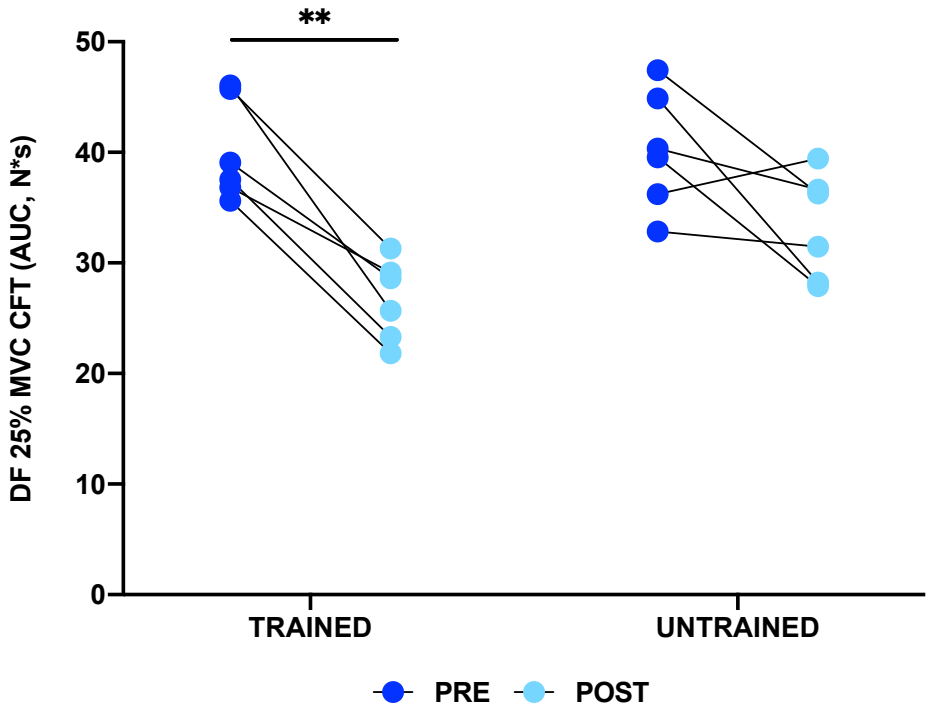


Figure 3.4 *Dorsiflexor (DF) complex force tracking (CFT; area under the curve, AUC (N*s)) data at 25% maximal voluntary contraction (MVC) pre- and post-motor control training (MCT) in the trained and untrained limb. **, $p < 0.01$.*

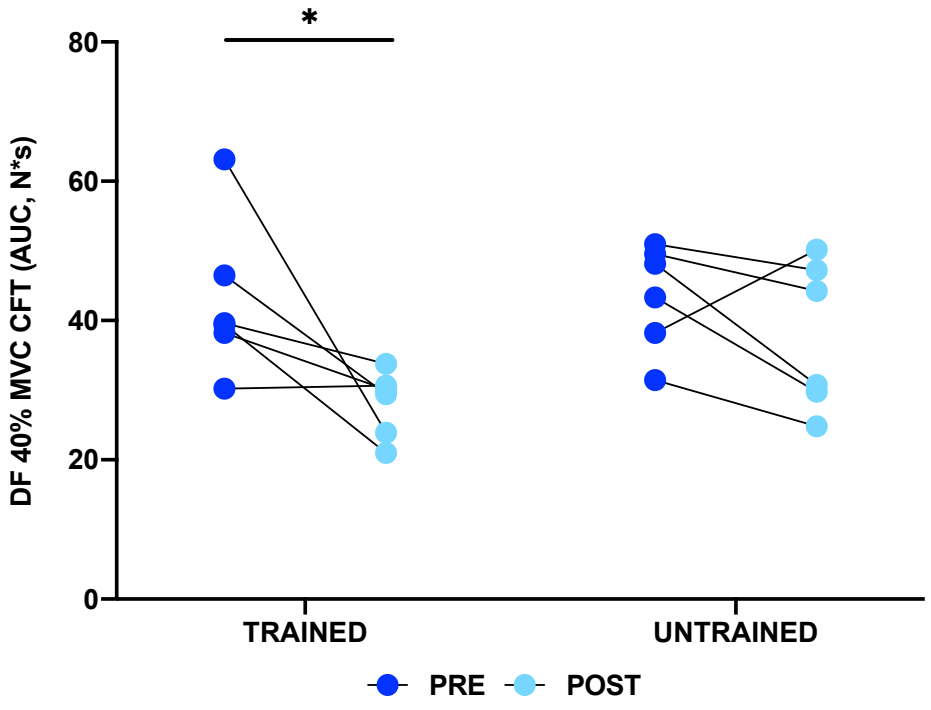


Figure 3.4 *Dorsiflexor (DF) complex force tracking (CFT; area under the curve, AUC (N*s)) data at 40% maximal voluntary contraction (MVC) pre- and post-motor control training (MCT) in the trained and untrained limb. *, $p < 0.05$.*

3.5. iEMG parameters

A total of 1,181 MUs were sampled at 25% MVC, from all muscles (VL and TA) investigated across both legs and timepoints. Tables 3.1. and 3.2. display the outputs from the multi-level, mixed effects linear models for VL (n = 4) and TA (n = 5) respectively. No interactions were observed with respect to outputs for TA, hence only a single a single beta (ß) coefficient and 95% CI are presented.

Table 3.1. Peripheral and central motor unit (MU) characteristics in the vastus lateralis (VL; *n* = 4) following motor control training (MCT).

Variable	**Interaction**	**Timepoint (pre *vs.* post, T leg)**				**Timepoint (pre *vs.* post, UT leg)**			
	p-value	ß	95% CI [lower]	95% CI [upper]	*p*-value	ß	95% CI [lower]	95% CI [upper]	*p*-value
Peripheral									
MUP area (µV)	**0.001**	**291.803**	**166.234**	**417.371**	**< 0.001**	**-227.166**	**-352.481**	**-101.851**	**< 0.001**
MUP turns	**0.001**	**0.524**	**0.185**	**0.863**	**0.002**	**-0.677**	**-1.016**	**-0.338**	**< 0.001**
NFPS jitter (µs)	**0.002**	**-3.551**	**-5.737**	**-1.364**	**0.001**	**4.852**	**2.647**	**7.057**	**< 0.001**
Central									
FR CoV (%)	**0.024**	**-1.869**	**-3.425**	**-0.313**	**0.019**	**1.746**	**0.206**	**3.285**	**0.026**
		Timepoint (pre *vs.* post)							
FR (Hz)	-	0.336	-0.064	0.736	0.099	-	-	-	-

No significant differences at baseline between the trained and untrained leg were observed. No interaction effect is indicated by '-'. CI, confidence interval; CoV, coefficient of variation; FR, firing rate; Hz, hertz; MUP, motor unit potential; NFPS, near fibre potential segment; T, trained; µs, microseconds; UT, untrained; µV, microvolts. Bold, statistical significance (p < 0.05).

Table 3.2. Peripheral and central motor unit (MU) characteristics in the tibialis anterior (TA; $n = 5$) following motor control training (MCT).

Variable	**Interaction**	**Time effect (pre *vs.* post)**			
	p-value	ß	95% CI [lower]	95% CI [upper]	*p*-value
Peripheral					
MUP area (μV)	-	***248.096***	***160.967***	***335.225***	***< 0.001***
MUP turns	-	0.227	-0.027	0.480	0.079
NFPS jitter (μs)	-	**-4.197**	**-6.022**	**-2.371**	**< 0.001**
Central					
FR CoV (%)	-	-0.749	-2.058	0.560	0.262
FR (Hz)	-	0.326	-0.278	0.929	0.290

No interaction effects (indicated by '-') were observed for all parameters, therefore only a single beta (ß) coefficient value and 95% CI are presented. CI, confidence interval; CoV, coefficient of variation; FR, firing rate; Hz, hertz; MUP, motor unit potential; NFPS, near fibre potential segment; μs, microseconds; μV, microvolts. Bold, statistical significance ($p < 0.05$). Italics, significant difference at baseline between legs for MUP area ($p = 0.009$) only.

3.5.1. Motor unit potential area and neuromuscular junction discharge variability

MUP area in VL (Figure 3.20.) displayed a significant interaction effect ($p = 0.001$) post-MCT, with increased MUP area in the trained leg (ß = 291.803; 95% CI = 166.234 – 417.371; $p < 0.001$) and decreased MUP area in the untrained leg (ß = -277.166; 95% CI = -352.481 – -101.851; $p < 0.001$). Similarly, the number of MUP turns (Figure 3.21.; interaction, $p = 0.001$) increased in the trained leg (ß = 0.524; 95% CI = 0.185 – 0.863; $p = 0.002$) with a reduced number of turns observed in the untrained leg (ß = -0.677; 95% CI = -1.016 – -0.338; $p < 0.001$). Likewise, TA MUP area (Figure 3.22.) increased in both legs following MCT (ß = 248.096; 95% CI = 160.967 – 335.225; $p < 0.001$), but with

non-significant evidence of an elevated number of MUP turns (Figure 3.23.; ß = 0.227; 95% CI = -0.027 – 0.480; $p = 0.079$).

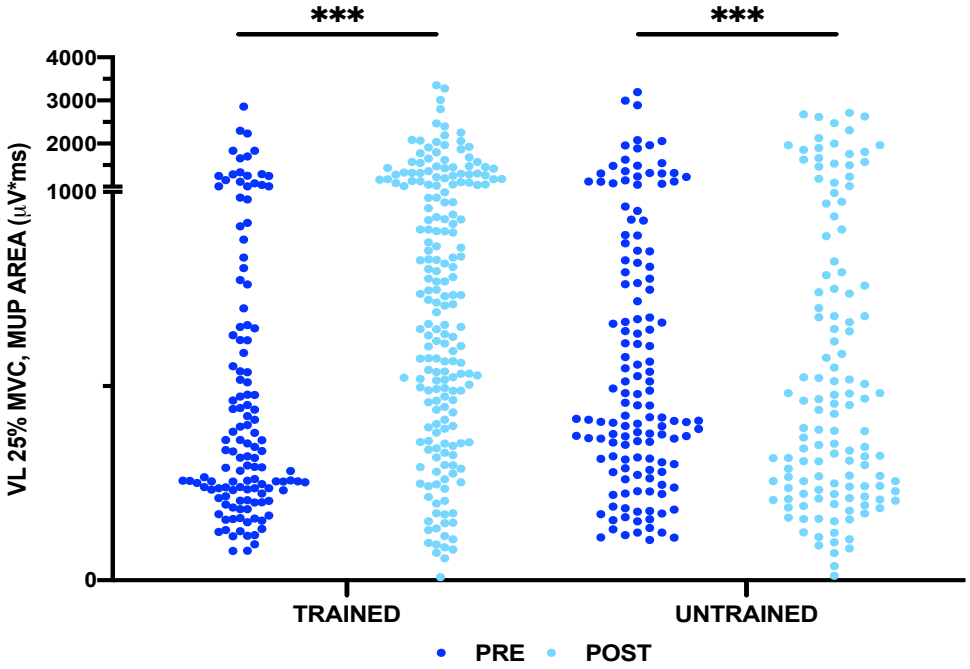


Figure 3.20. *Motor unit potential (MUP) area (μV*ms) in the vastus lateralis (VL) at 25% maximal voluntary contraction (MVC), pre- and post-motor control training (MCT) in the trained and untrained limb. Data is presented for whole motor unit (MU) pool (n = 4). ***, p < 0.001.*

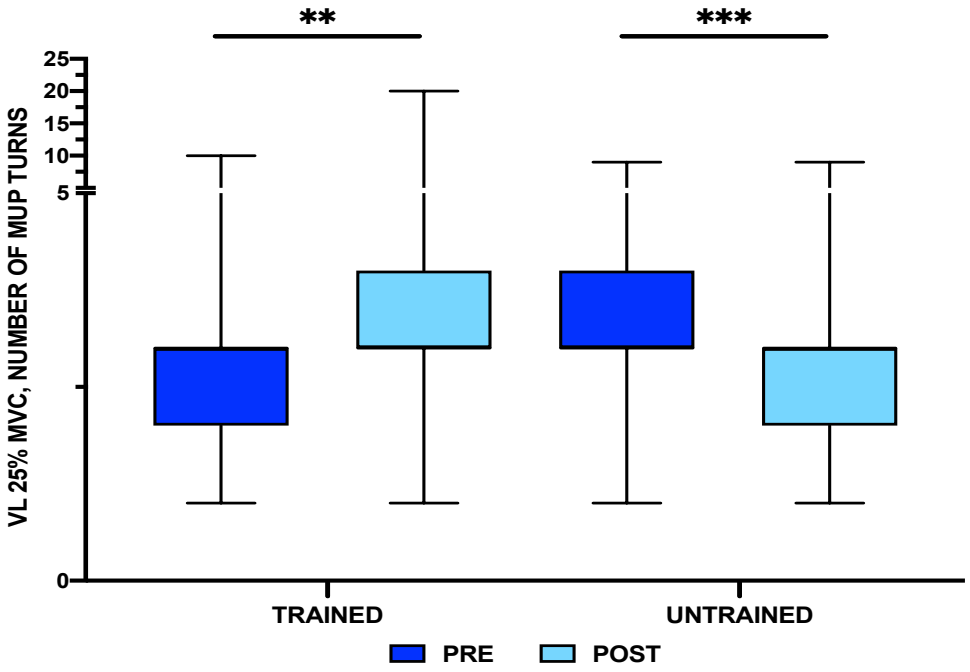


Figure 3.21. *Motor unit potential (MUP) turns in the vastus lateralis (VL) at 25% maximal voluntary contraction (MVC), pre- and post-motor control training (MCT) in the trained and untrained limb. Data is presented for whole motor unit (MU) pool (n = 4), whiskers span from minimum to maximum values. **, p < 0.01; ***, p < 0.001.*

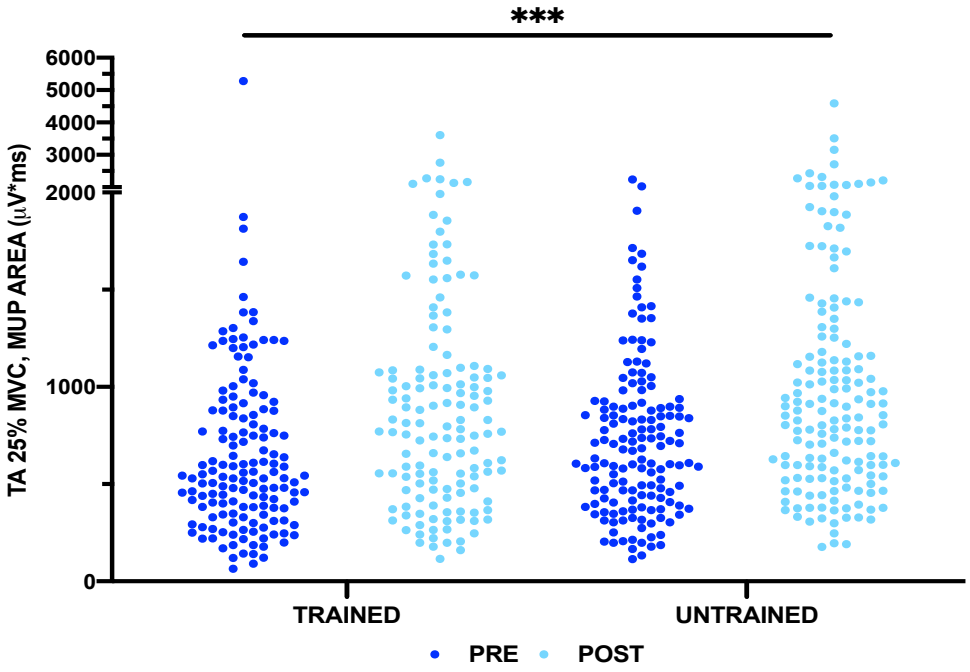


Figure 3.22. *Motor unit potential (MUP) area (μV*ms) in the tibialis anterior (TA) at 25% maximal voluntary contraction (MVC), pre- and post-motor control training (MCT) in the trained and untrained limb. Data is presented for whole motor unit (MU) pool (n = 5). ***, p < 0.001.*

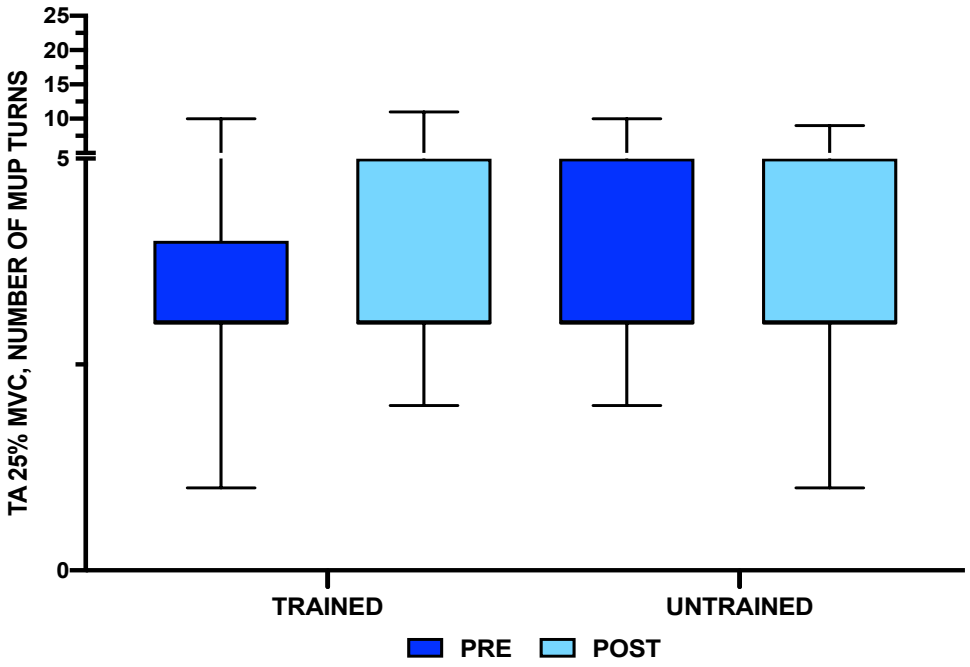


Figure 3.23. *Motor unit potential (MUP) turns in the tibialis anterior (TA) at 25% maximal voluntary contraction (MVC), pre- and post-motor control training (MCT) in the trained and untrained limb. Data is presented for whole motor unit (MU) pool (n = 5), whiskers span from minimum to maximum values.*

VL near fibre potential segment (NFPS) jitter (Figure 3.24.) exhibited a significant interaction effect ($p = 0.002$) following MCT, with reduced NFPS jitter in the trained leg (ß = -3.551; 95% CI = -5.737 – -1.364; $p = 0.001$) and increased NFPS jitter in the untrained leg (ß = 4.852; 95% CI = 2.647 – 7.057; $p < 0.001$). Although no interaction was present in TA ($p > 0.05$), NFPS jitter significantly reduced post-MCT (Figure 3.25.; ß = -4.197; 95% CI = -6.022 – -2.371; $p < 0.001$).

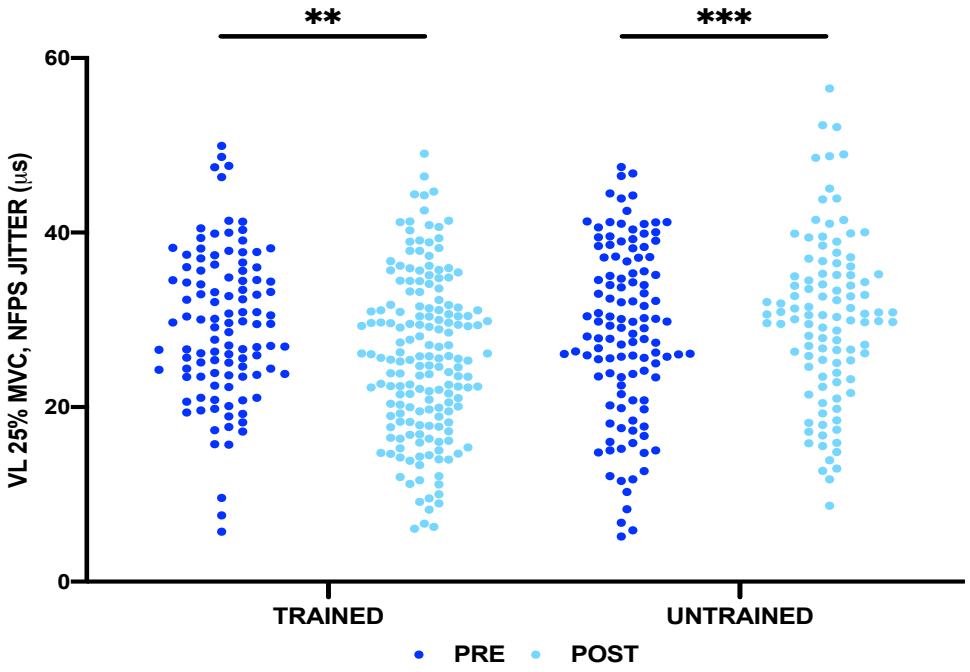


Figure 3.24. *Near fibre potential segment (NFPS) jitter (µs) in the vastus lateralis (VL) at 25% maximal voluntary contraction (MVC), pre- and post-motor control training (MCT) in the trained and untrained limb. Data is presented for whole motor unit (MU) pool (n = 4). **, p < 0.01; ***, p < 0.001.*

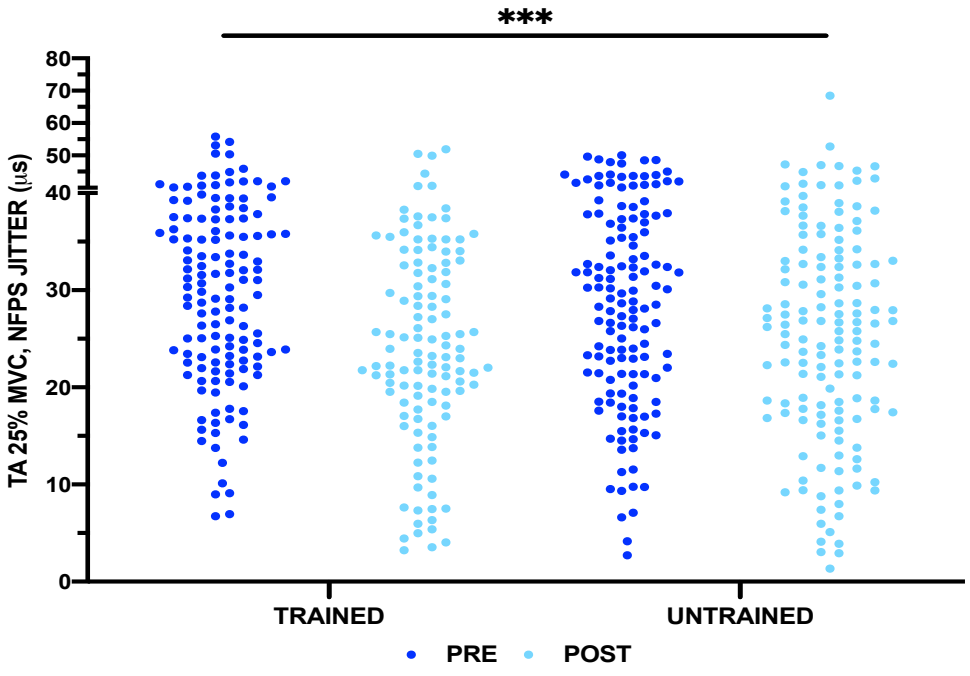


Figure 3.25. *Near fibre potential segment (NFPS) jitter (µs) in the tibialis anterior (TA) at 25% maximal voluntary contraction (MVC), pre- and post-motor control training (MCT) in the trained and untrained limb. Data is presented for whole motor unit (MU) pool (n = 5). ***, p < 0.001.*

3.5.2. Motor unit firing rate and firing rate variability

MU FR in both VL (ß = 0.336; 95% CI = -0.064 – 0.736; p = 0.099) and TA (ß = 0.326; 95% CI = -0.278 – 0.929; p = 0.290) remained unchanged following 4 weeks MCT (see Figures 3.26. and 3.27.).

With respect to FR variability (determined as FR CoV), a significant interaction effect (p = 0.024) was observed in VL (Figure 3.28.), with FR variability reducing in the trained leg (ß = -1.869; 95% CI = -3.425 – -0.313; p = 0.019) but increasing in the untrained leg (ß = 1.746; 95% CI = 0.206 – 3.285; p = 0.026). FR variability remained unchanged in TA (Figure 3.29.) post-MCT (ß = -0.749; 95% CI = -2.058 – 0.560; p = 0.262).

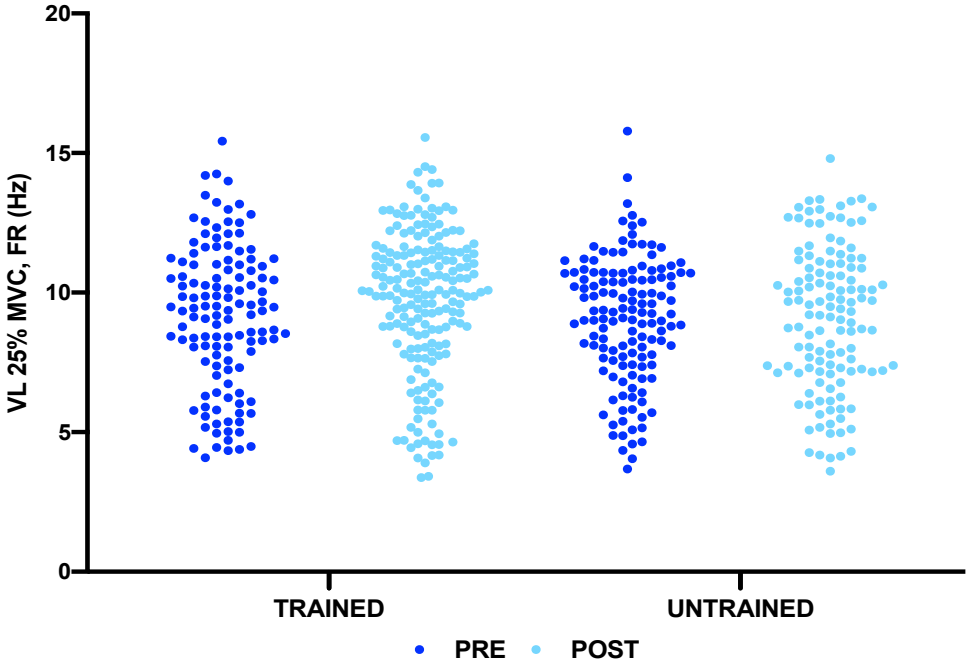


Figure 3.26. *Motor unit (MU) firing rate (FR; Hz) in the vastus lateralis (VL) at 25% maximal voluntary contraction (MVC), pre- and post-motor control training (MCT) in the trained and untrained limb. Data is presented for whole MU pool (n = 4).*

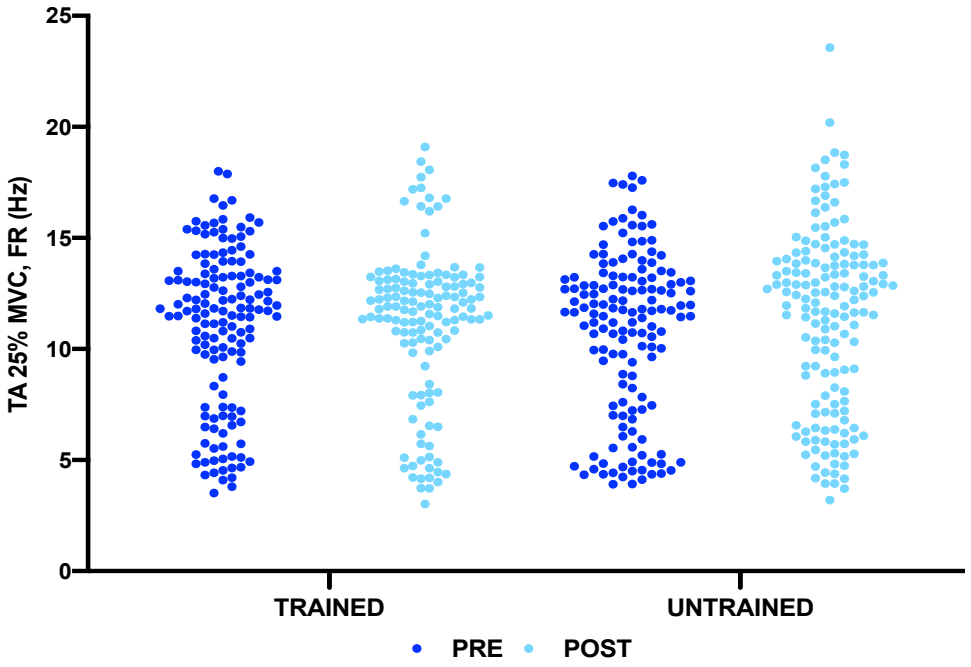


Figure 3.27. *Motor unit (MU) firing rate (FR; Hz) in the tibialis anterior (TA) at 25% maximal voluntary contraction (MVC), pre- and post-motor control training (MCT) in the trained and untrained limb. Data is presented for whole MU pool (n = 5).*

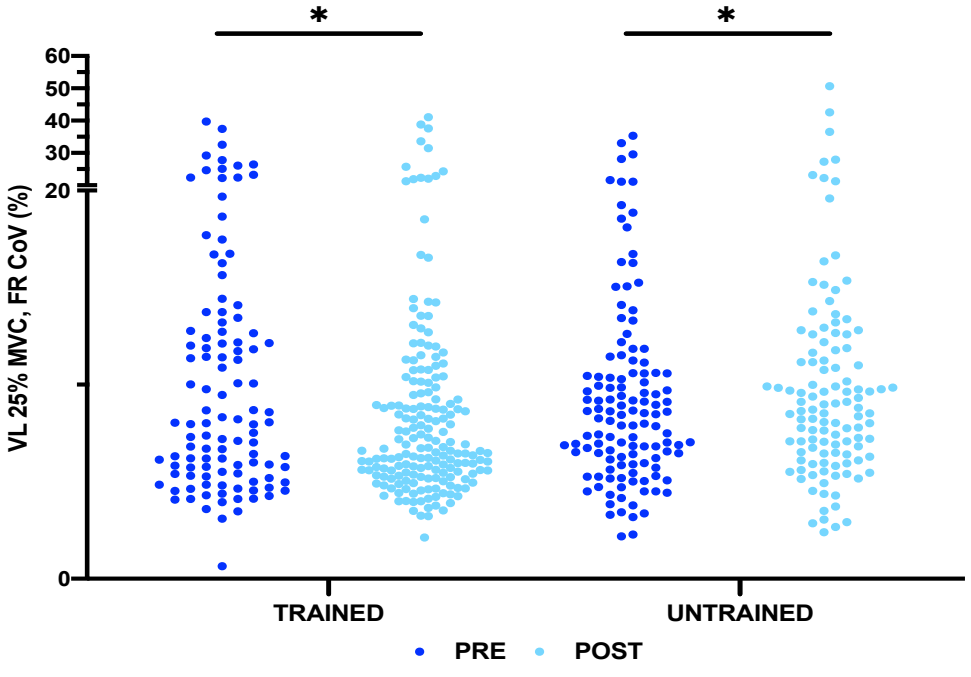


Figure 3.28. *Motor unit (MU) firing rate (FR) variability (coefficient of variation, CoV (%)) in the vastus lateralis (VL) at 25% maximal voluntary contraction (MVC), pre- and post-motor control training (MCT) in the trained and untrained limb. Data is presented for whole MU pool (n = 4). *, $p < 0.05$.*

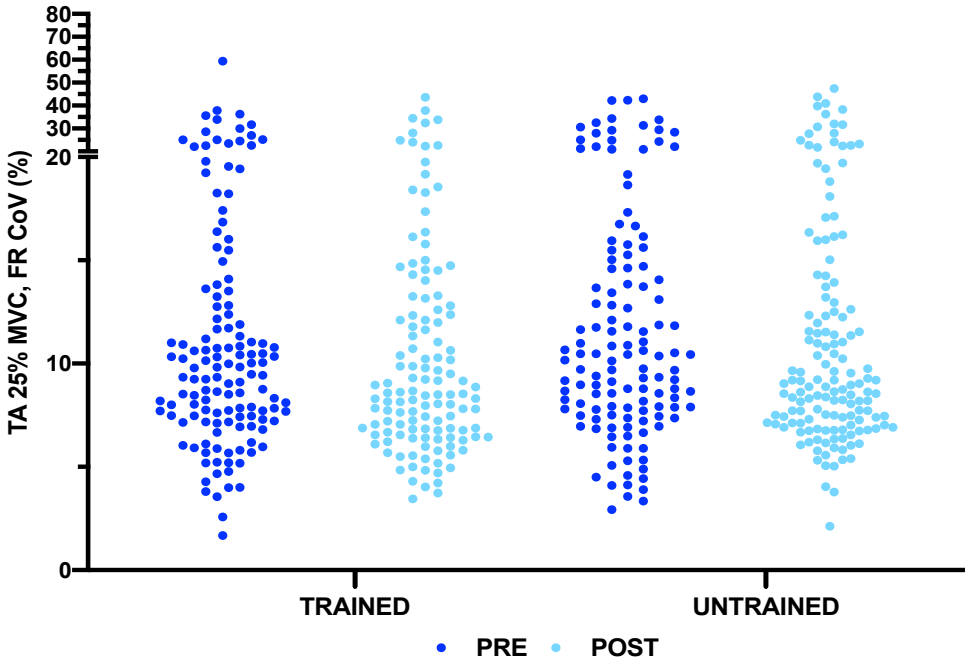


Figure 3.29. *Motor unit (MU) firing rate (FR) variability (coefficient of variation, CoV (%)) in the tibialis anterior (TA) at 25% maximal voluntary contraction (MVC), pre- and post-motor control training (MCT) in the trained and untrained limb. Data is presented for whole MU pool (n = 5).*

4. Discussion

The aim of the current study was to investigate the efficacy of a targeted 4-week MCT programme, on levels of MC, in the KE and DF, and on MU parameters in both the VL and TA muscles. We hypothesised in young, healthy volunteers, 4 weeks of MCT would not elicit changes in maximal voluntary force but would improve MC (assessed through FS and CFT) in both of the trained muscles, in conjunction with decreased FR variability. In summary, maximal force and FS remained unchanged for both the KE and DF following MCT. Performance of CFT tasks improved, suggesting better levels of MC in the trained leg for the KE at 10, 25 and 40% MVC, with improvements also observed in the trained DF at 25 and 40% MVC. Interestingly, CFT also improved in the untrained leg at 10% MVC for both KE and DF, with improvements also seen at 40% MVC in the KE. Through assessing single MU adaptations to MCT via iEMG, we describe both central and peripheral mechanisms which may contribute to the improvement in MC in young, healthy participants following MCT.

4.1. Muscle strength and physical performance

Maximal voluntary force remained unchanged in both the KE and DF across both legs, in line with our hypothesis. In the trained leg, the KE were, however, significantly stronger than in the untrained leg both at baseline and at follow-up testing potentially due to a presence of limb dominance (Balogun & Onigbinde, 1992). This demonstration of an absence of increased force production following training is, however, not in direct agreement with others. For example, in older adults, 8 weeks of low intensity RET (30% 1-RM, not dissimilar to the intensity of MCT) led to increased MVC of the KE, although no difference in MVC of

the elbow flexors (Kobayashi et al., 2014). Similarly, 16 weeks of KE training at the same intensity as that reported by Kobayashi and colleagues also resulted in significant increases in KE strength in older adults (Tracy & Enoka, 2006). Importantly, these increases were evident after just 2 weeks of training and as such cannot be attributed solely to the longer training duration in this study (Tracy & Enoka, 2006). Although low intensity RET (i.e. ~20 - 40% 1-RM) can induce increases in muscle strength (Keen et al., 1994; Hortobagyi et al., 2001; Kobayashi et al., 2014), this notion remains inconclusive with Moore et al., reporting unchanged isometric EF MVC force following 8 weeks unilateral EF training in young individuals at 50% 1-RM (Moore et al., 2004). Improvements in muscle strength have not only been seen following "traditional" RET programmes with Christou and colleagues reporting increased muscle strength following 20 weeks of martial arts training (Christou et al., 2003). It must however be noted that many of the positive reports outlined above were in older adults, many of whom were previously sedentary; a population of individuals arguably having the most to gain from being physically active (McPhee et al., 2016). As our current study recruited a population of physically active, healthy young individuals, and although not a main aim of this study, a lack of increase in muscle strength with our low intensity MCT did not come as a surprise. Additionally, strength increases may have been absent in the current study due to 1) training load (%MVC) was not increased throughout training and 2) contractions were maintained for a short period of time. Despite this, older adults may display increases in muscle strength following MCT. As previously stated, reduced PA and exacerbated sedentarism is evidenced with increasing age (McPhee et al., 2016), and with the concurrent declines in muscle mass, strength

and impairment of the neuromuscular system (Mitchell et al., 2012; Piasecki et al., 2016*a*), increased muscle strength in older adults may be a positive resultant factor of MCT (a future direction of this research).

In the current study, an absence of increased muscle strength should not point towards the training intervention being unsuccessful. Indeed, although increased maximal strength is of functional benefit, especially for older adults, through increasing muscle force production which is substantially reduced through the detrimental effects of sarcopenia (Mitchell et al., 2012; Wilkinson et al., 2018), other aspects of neuromuscular function are equally important for functional outcomes (i.e. MU remodelling (Piasecki et al., 2016*a*) and alterations to sensory feedback mechanisms which would influence control of submaximal voluntary muscle contractions (Hortobagyi et al., 2001)), with gains in maximal strength even shown to not be related to some measures of muscle functional capacity (Chandler et al., 1998). In support of the proposition of aspects of neuromuscular function, beyond maximal strength being important for functional capacity, Chandler and colleagues examined the impact of a 10-week lower extremity strength training programme (3x per week using a TheraBand and body weight to provide resistance) in older adults (Chandler et al., 1998). Although gains in strength were associated with improved gait speed, chair rise performance and confidence regarding fall avoidance in individuals who were more impaired, there were no associations between increased muscle strength and improvements in balance, endurance performance or disability measures (Chandler et al., 1998). The authors of this work attributed the absence of association between these measures to be due to the lack of specific training seemingly needed to

improve such measures (i.e. endurance training to improve endurance capacity) (Chandler et al., 1998).

Balance in older age has been shown to deteriorate (Izquierdo et al., 1999*a*; Hess & Woollacott, 2005), with particular importance directed to neuromuscular mechanisms (Zech et al., 2010), thus impacting maintenance of position, movement stabilisation and/or reaction to external disturbances (Izquierdo et al., 1999*a*). Ultimately, impairments in balance with increasing age exposes older individuals to a greater risk of falls, with 50% of those over 80 years falling each year (Hess & Woollacott, 2005). Evidence has highlighted that older adults have elevated measures of sway for both single and double leg static standing balance and response to alterations in visual surroundings and postural perturbations (Maki et al., 1990; Izquierdo et al., 1999*a*). We would, therefore, expect older adults to have worse balance scores compared to our young experimental group, and believe it is reasonable to hypothesise that MCT would lead to improved balance, specifically in the trained leg, in older adults. Although the evidence from utilising RET included above points towards increased MVC force and some measures of physical function through training, it is important to note the MCT intervention used in the current study was aimed to be more accessible training programme for older adults (thus conducted at lower training intensities) making it a more specific and targeted approach conducted for improving MC.

4.2. Force steadiness and complex force tracking

As discussed in section 1.5., MC, specifically in this thesis focussing on the ability to control voluntary muscle force, declines with advancing age alongside decrements in muscle strength and the function of the neuromuscular system

(Enoka et al., 2003; Piasecki et al., 2016*a*; Wilkinson et al., 2018). Typically, FS (the ability to maintain a submaximal force level around a set value (Beck et al., 2011)) and subsequent calculation of SD and/or CoV of force has been used to assess FS, with older compared to younger adults displaying greater force variation (Enoka et al., 2003; Hunter et al., 2016) in both the upper (see section 1.5.1.1.) (Galganski et al., 1993; Keen et al., 1994) and lower (see section 1.5.1.2.) (Carville et al., 2007; Dewhurst et al., 2007) limbs. The current study utilised two different force tracking tasks, varying in difficulty, in order to assess levels of basic neuromuscular function and MC. In-line with previous literature, KE and DF FS exhibited a general pattern with lower contraction intensities (10% MVC) eliciting greater force fluctuations (greater CoV values), which declined with increasing contraction intensity. Despite this, FS remained unchanged following MCT in both the KE and DF, although the KE of the trained leg had lower CoV of force at 25% MVC compared to the untrained leg, with a strong trend exhibited at baseline and significance achieved at follow-up testing. When examining CFT, a significant main effect of time (pre- to post-MCT) was exhibited at each contraction intensity for the KE and DF. More specifically, within the trained leg, CFT significantly improved in the KE at each of the target levels, with the trained leg for the DF improving at 25% and 40% MVC.

With respect to previous literature, Beck and colleagues also saw no improvements to KE FS in young participants following RET, although FS was assessed at a much higher contraction intensity (80% MVC) than what was used in the current study, and may explain why the authors (Beck et al., 2011) saw a

lack of improvement, with improvements in FS seeming to be more pronounced at lower contraction intensities (Enoka et al., 2003). Furthermore, Keen et al., demonstrate limited improvements in FDI FS within young participants despite older counterparts improving significantly following strength training, especially at the lowest (2.5% MVC) contraction intensity (Keen et al., 1994). Although we saw no improvements in FS, our results seem to be in-line with the literature with limited improvements observed following training in young adults with respect to FS (Keen et al., 1994; Beck et al., 2011), which may be explained by an absence of neuromuscular deficit in healthy young compared to older adults (Piasecki et al., 2016*a*; Wilkinson et al., 2018).

Importantly, the current study utilised isometric contractions in the form of CFT for the MCT intervention, with the CFT task presenting with an oscillating, rather than straight sustained, target line. For tasks varying in muscle force to match the intended profile (such as CFT), the muscle needs to accommodate for varying rise and fall times in force generated by active MUs for appropriate muscle control (Duchateau & Enoka, 2008). During isometric contractions of fluctuating force, the recruitment and subsequent de-recruitment of MUs needs to be aligned to match the desired trajectory to increase and decrease force (Duchateau & Enoka, 2008). As such, both MU recruitment and de-recruitment requires different control strategies, leading to some individuals experiencing difficulty when decreasing force (Duchateau & Enoka, 2008). Resultingly, the fluctuation in force during CFT may contribute to positive alteration of MC strategies, hence observing improvements in CFT and MC following training.

When focussing on the untrained limb, we also saw improvements following MCT in CFT contractions at 10% and 40% MVC in the KE, with the DF improving at 10% MVC only. These results perhaps point towards the phenomenon of cross education (CE), typically described as the gain in strength/skill in the opposite, untrained limb, which is specific only to the contralateral homologous muscle, through alterations to the nervous system (Lee & Carroll., 2007; Hendy & Lamon, 2017).

A meta-analysis by Munn and colleagues estimated that a 7.8% increase in strength in the contralateral limb is evidenced, which was equivalent to a 35% increase in strength in the trained limb, in unilateral training studies which included an exercise and control group with a training intensity greater than 50% MVC for a period longer than 2 weeks (Munn et al., 2004). The phenomenon of CE also presents when examining unilateral strength training during a period of immobilisation, with Farthing et al., demonstrating unilateral training during a 3-week immobilisation period, led to no changes in muscle strength and thickness in the immobilised limb compared to the "pure" immobilisation group (Farthing et al., 2009); although, here, the role of the nervous system was not quantified. Despite this, the potential of CE and attenuation of strength deficits in the immobilised limb is particularly attractive with respect to rehabilitation and especially in older adults who may not fully recover from a period of immobilisation (Suetta et al., 2009).

CE is thought to occur via alterations to neural processes (as detailed in Ruddy & Carson, 2013), with 2 theoretical models being proposed; the first of these

being the “bilateral-access” or “bilateral transfer” hypothesis. The bilateral-access model proposes that motor engrams developed in the ipsilateral limb during unilateral training, may become bilaterally accessed with the movement control centres being “available” to both limbs (Ruddy & Carson, 2013; Hendy & Lamon, 2017). The second “cross activation” theory, describes an increase in the bilateral cortical excitability through performing unilateral exercise (Ruddy & Carson, 2013) (Hendy & Lamon, 2017). Although the current study did not utilise supraspinal testing methodologies (such as transcranial magnetic stimulation, TMS) to assess cortical excitability, it still remains possible that MCT could elicit CE effects whereby the untrained limb exhibits greater control of movement through adaptation in motor areas predominately responsible for the control and execution of movements of the trained limb (Lee & Carroll, 2007); although further research is needed to confirm this.

Despite the present study failing to observe enhanced FS following MCT, the importance of FS with respect to activities of daily living should not be dismissed. Commonly, FS has been highlighted as a critical explanatory variable with respect to muscular performance of tasks including walking (Davis et al., 2020), tremor (Kavanagh et al., 2016; Keogh et al., 2019), and risk of falls in older adults (Carville et al., 2007). A recent study by Davis and colleagues examined FS in the PF and DF at 10 and 20% MVC in individuals who presented with multiple sclerosis (MS) and those who did not (Davis et al., 2020). The authors report that individuals who had MS presented with worse FS compared to the control group in the DF at 20% MVC, with no differences in the PF (Davis et al., 2020). Importantly, a reduced walking distance during a 6-minute walk

test and increased time to walk 25 feet was associated with a greater CoV of force during submaximal contractions in the PF and DF for those with MS, with reduced walking distance in the control group being associated with DF FS and variation of common input to the PF during steady contractions (Davis et al., 2020). Although MS is a neurological disorder impacting both the central and peripheral nervous systems (Davis et al., 2020), the age-related decline in the neuromuscular system presents with similar mobility-impairing symptoms which ultimately impacts quality of life (Mitchell et al., 2012; Wilkinson et al., 2018); thus, the impact of MCT on FS should be examined in older adults to determine whether the more targeted approach (*vs.* traditional RET, for example) leads to improvements in MC.

4.3. Motor unit alterations

Age-related declines in neuromuscular function are increasingly a focus of research, with emphasis on considering both the decline in muscle mass and MU loss in tandem (Piasecki et al., 2016*a*; Wilkinson et al., 2018). As discussed in section 1.4., MU number declines with advancing age, evidenced in both post-mortem studies (Tomlinson & Irving, 1977; Lexell et al., 1988) and through advancements in EMG (Piasecki et al., 2016*a*, 2016*c*, 2018*a*), with larger MUPs found in older compared to younger individuals, indicating the presence of MU remodelling to preserve muscle function (Piasecki et al., 2016*a*, 2018*a*). Importantly, sarcopenic individuals seem to display smaller MUPs compared to non-sarcopenic and pre-sarcopenic (+26% and +44% respectively) individuals (Piasecki et al., 2018*a*), suggesting a failure to expand MU size distinguishes sarcopenic from non-sarcopenic older men, through excessive fibre loss when reinnervation of denervated fibres is unable to occur (Piasecki et al., 2018*a*). As

the control of muscle force is expressed at the MU level (Keen et al., 1994), it is plausible to suggest that the age-related declines in MU number and MU remodelling likely contribute to declines in MC with advancing age (Enoka et al., 2003). Despite this knowledge, there is absence within the literature investigating specific MU adaptations, especially in larger muscle groups important for ambulation, with respect to MC and ageing.

The current study utilised the novel technique of iEMG to assess both central and peripheral neuromuscular adaptations at the single MU level, the smallest functional unit of the human neuromuscular system (Sherrington, 1925). Compared to central adaptions (described below), much less is known with respect to peripheral adaptations to the neuromuscular system following interventions aimed to improve MC. Here, we demonstrate that VL MUP area increased in the trained leg with decreases in the untrained leg, alongside increases in TA MUP area across both legs. Such increases in MUP area were associated with significant increases in the number of VL MUP turns (defined as a change in direction of the waveform of at least 25 μV (Piasecki et al., 2016*c*)) in the trained leg but decreases in the untrained leg, although weaker evidence was provided for TA. We additionally observed a reduction in NMJ transmission instability (NFPS jitter; which tracks temporal shifts in segments of consecutive NF MUPs over the NF MUP duration (detailed in AbdelMaseeh & Stashuk, 2017) in the trained leg for VL and across both legs for TA. Similar to MUP area, we again highlight bilateral differences in VL with respect to NFPS jitter increasing in the untrained leg.

Alterations to NMJ transmission instability and MUP area following MCT may be dictated by ionic changes within the muscle, leading to potential adaptions to sarcolemmal RMP but also to the exchange of ions during AP generation (MacIntosh et al., 2012). Resultingly, the release of acetylcholine from the presynaptic head, Na^+/K^+ pump activity, or modification to Na^+ and/or K^+ intracellular and/or extracellular concentrations may subsequently alter AP transmission (Allen et al., 2008), which could lead to alterations in NFPS jitter and MUP area following MCT; although further research is needed to determine this.

Central adaptions to the neuromuscular system, that being MU FR and MU FR variability assessed in the present study, are addressed to a greater extent within the literature. Although, in young participants, we display no alterations to FR in both VL and TA, this is not to suggest we would observe similar results in older adults. With advancing age, the influence of MU remodelling leads to larger MUs becoming activated at lower force levels and FRs (Piasecki et al., 2016*a*; Oomen & van Dieen, 2017), thus contributing to an age-related irregularity of MU FR (Enoka et al., 2003); likely leading to associated declines in MC through maladaptation of FS. Importantly, differences in MU FR emerge when assessing dynamic muscle contractions, highlighting greater irregularity in MU FR during eccentric rather than concentric contractions (Enoka et al., 2003), which has the ability to explain differences exhibited in the quadriceps between older adults who were “fallers” and “non-fallers” during eccentric contractions (Carville et al., 2007).

Despite no alterations to FR exhibited in the current study, Del Vecchio and colleagues report, in young individuals, MU discharge rate increased in TA during the "plateau phase" of submaximal isometric contractions (at 35, 50 and 70% MVC) following 4 weeks strength training (consisting of maximal ballistic contractions and isometric contractions at 75% MVC; a greater training intensity and variation of muscle contractions "types" than that used in the current study) (Del Vecchio et al., 2019). The authors further highlight a reduction in the relative MU recruitment threshold following strength training, indicating earlier recruitment of MUs during isometric contractions to produce the necessary force trajectory (Del Vecchio et al., 2019). In FDI, Kornatz and colleagues highlight older adults exhibited improved FS in the first 2 weeks of training with a light load (10% 1-RM) with no further improvements seen at 4 weeks utilising a heavier load (~70% 1-RM) (Kornatz et al., 2005). Correlation analysis revealed reduced force fluctuations during lengthening and shortening contractions, in addition to improvements in manual dexterity, was associated directly to declines in FDI MU discharge variability (Kornatz et al., 2005). Laidlaw and colleagues report older adults to have impaired FS during isometric and slow anisometric contractions compared to young counterparts, especially at low contraction forces (Laidlaw et al., 2000). The authors highlight that although MU discharge rates (reported as mean values) were not different between the groups, older individuals presented with greater discharge rate variability which is likely to contribute to hindered performance of steady contractions (Laidlaw et al., 2000).

The use of computational models (Moritz et al., 2005) has allowed for manipulation of key MU parameters, naming FR and FR variability, in order to examine the influence they have on FS. Subsequently, Mortiz and colleagues initially sampled 38 MUs in the FDI muscle from 18 young participants across a large range of contraction intensities (4-85% MVC), thus encompassing MUs with low and high recruitment thresholds (Moritz et al., 2005). The authors highlight a main finding that with increasing index finger force, FDI discharge rate variability exponentially reduced, corresponding with improved simulated force fluctuations when entered into the computational model (Moritz et al., 2005). These simulated data are consistent with experimental (Laidlaw et al., 2000) and other simulation observations (Enoka et al., 2003). This suggests MU discharge variability to be a, if not the, key physiological parameter compared to other MU parameters to influence FS (Vila-Chã & Falla, 2016) and the age-related decline in MC.

Through utilising 6 weeks (3 x per week) strength training (60-85% 1-RM) or endurance training (50-70% heartrate max), Vila-Chã and Falla highlighted FS improved by 27.2% with MU discharge variability (the variation in the time between consecutive MUPs) also reducing in both VL and vastus medialis (VM) following strength training only (Vila-Chã & Falla, 2016). Despite MU discharge variability reducing in both of the investigated vastii muscles, the reduction of MU discharge variability was only significantly correlated with improvements in FS for VM only at both 20% and 30% MVC (Vila-Chã & Falla, 2016). In the present study, we demonstrate VL FR variability to reduce post-MCT in the trained leg but increase in the untrained leg, although no alterations

to FR variability were observed in TA following MCT. As MU discharge variability and force fluctuations are governed by central descending pathways modulated by common inputs to the MU pool (Taylor et al., 2003; Vila-Chã & Falla, 2016), we suggest that these central adaptions to MU FR variability may be specific to the trained limb only as evidenced through the reduction in MU FR variability in the trained but not untrained VL, however, further research in a larger population size, in older adults and different muscle groups is needed to confirm this.

4.4. Strengths, limitations and future directions

A strength of the present study was the timing efficacy of the MCT intervention, that being the training period itself only being 4 weeks which has relevance and application to prehabilitation (Durrand et al., 2019) to limit muscle functional decline post-surgery, and each training session lasted only ~20 minutes occurring 3x per week. A major barrier in today's society to exercise/PA is a lack of recreational time (Salmon et al., 2003), thus with MCT being only ~20 minutes in duration, this could, to some extent, combat this barrier. Secondly, the CFT tasks (rather than FS tasks during sustained non-fluctuating contractions) used for MCT are arguably more applicable to daily movements (e.g. rising from a chair) due to the fluctuations in the force trace requiring greater muscle coordination. A third strength of this work was the use of intramuscular EMG and near-fibre analysis to identify single MU characteristics from a range of muscle depths in participants pre- and post-MCT, therefore affording greater insight into central and peripheral adaptions to MCT at a single MU level. Finally, we believe the use of within-participant controls to be of benefit to avoid high levels of inter-individual variability with regards to such

tasks (FS and CFT) used in the current study. Completing testing within the same person, normalised to MVC of each target muscle, can help avoid this issue.

A limitation of the study was the small sample size, with some parameters only having data presented for 4 participants, and only young participants being included. However, these circumstances were out of our control due to the COVID-19 pandemic, meaning the originally planned age-comparison aspect of the study was not possible and 3 additional young participants who were enrolled in the study could not complete. A second limitation is that all MU data presented was recorded at 25% MVC during a steady isometric contraction, making it possible that smaller/medium MUs were sampled from the whole MU pool (Henneman et al., 1965; Piasecki et al., 2016*c*). The observed MU adaptions recorded during 25% MVC were associated with improvements in MC, at all (10, 25 and 40% MVC) contraction intensities from CFT tasks. Despite this, contractions at 25% MVC allow sampling of MUs from a mid-range contraction intensity with iEMG data being difficult to decompose if sampled during CFT contractions due to the oscillating force trace. Thirdly, it is not possible to directly measure the number of MUs *in vivo* in humans (Piasecki et al., 2016*a*), therefore the sampled MUs in the current study are limited by the capture area of the recording electrodes, however MU characteristics do not differ from proximal to distal regions of VL are a representation of the pool of MUs for the muscles investigated (Piasecki et al., 2018*b*). Finally, despite providing great detail, a limitation of iEMG is that there is a lack of matching MUs pre- and post-intervention as it is not possible to track the same MUs across sessions, meaning different populations of MUs could be sampled pre- and post-training.

The addition of HD-sEMG, in conjunction with iEMG, may add clearer insight of training-induced adaptations of MU properties of the same MU (Martinez-Valdes et al., 2017).

Future directions for the current study will focus on applying the MCT intervention within older adults, thus determining whether greater beneficial effect to MC and MU alterations are seen in older adults compared to what we observed in young participants. A second direction would be to determine the effect of MCT in other muscles important for dexterity (i.e. FDI), which can become affected by tremor through older age (Kavanagh et al., 2016). Finally, as the training period we used (4 weeks) can be matched with the timings for prehabilitation periods prior to surgery (Durrand et al., 2019), a more clinically relevant approach could be to apply MCT to examine whether it preserves muscle function and control in the postoperative period.

4.5. Conclusions

To summarise, we highlight that a 4-week period of targeted MCT leads to improved MC at different contraction intensities, across different functionally important muscles (VL and TA), in both the trained and untrained legs, in young healthy participants. We demonstrate, for the first time, reduced NMJ discharge variability (a measure of peripheral neuromuscular function) following MCT, in the trained VL and across both TA muscles. Moreover, it is probable the central adaptation of reduced MU FR variability (in the trained VL only) likely aids explanation to improved MC post-MCT, hence improving coordination of muscle contraction; although no such adaptions presented in TA, highlighting the possibility for muscles to respond differently to training. These data in young

individuals provide promising insight in suggesting MCT may lead to substantial improvements or maintenance of MC in older adults, a future direction of this research, in order to aid and determine mechanistic insight into the plasticity of movement control across the lifespan.

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Appendices

Appendix 1.1. Participant information sheet



Division of Medical Sciences and Graduate Entry Medicine
School of Medicine

Participant Information Sheet

Study Title: Investigating age-related differences in motor control and neuromuscular parameters in response to motor control training.

Name of Investigators:

Dr Beth Phillips Miss Isabel Ely
Dr Mathew Piasecki

You have been invited to take part in a research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish to. Please take time to decide whether or not you wish to take part. Ask us if there is anything that is not clear or if you would like more information. If you decide to take part, you will be given a copy of your consent form and this leaflet.

Background:

With increasing age, it is evident that individuals experience frailty; principally due to the age-related decline in skeletal muscle mass, known as sarcopenia. Sarcopenia not only leads to weakness and decreased functional capacity, but also impacts quality of life, increases the risk of falls and fractures and reduces overall health status. We know that our muscles do not work independently and that the nerves that supply the muscle (known as motor units) are equally as important for optimal muscle function. Poor communication between the nerve and muscle may lead to smaller, weaker muscles which are more difficult to control. Reduced control of muscles (known as motor control) is known to impact fine motor movements, such as opening a jar or using cutlery, and also aspects such as balance; things which are useful to perform activities of daily living and also to maintain independence-which can often be lost with advancing age.

Therefore, the aim of this study is to investigate whether motor control and muscle function can be improved by exercise training specifically

targeting motor control, and if there are any age-related differences in the ability to improve this aspect of muscle function.

We aim to recruit 12 healthy volunteers aged 18-35 years and 12 healthy volunteers over 65 years to assess the efficacy of a 4-week (3 sessions per week) motor control training programme on differing aspects of muscle function.

Why have you been chosen?

In order for this study to be successful, healthy volunteers have been chosen who fit the entry criteria and do not have significant on-going medical problems. We are inviting 12 participants aged 18-35 years and 12 participants over 65 years to take part.

Do you have to take part?

No, it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time without giving a reason.

Would there be an inconvenience allowance?

There is an inconvenience allowance of £100 associated with this study which you would receive on completion of the study.

What does the study involve?

The location for this study is The Medical School at the Royal Derby Hospital Centre.
The study consists of:
1) a screening visit to assess your suitability for the study (~45 minutes),
2) a baseline visit to assess your muscle function and structure (~3 hours),
3) 4-weeks motor control training (3-sessions per week each lasting ~20 min),
4) a re-assessment visit where your baseline visit measures will be repeated.

Screening Visit
Prior to being enrolled onto the study you will be asked to attend the Medical School at approximately 9am for a screening visit to assess your suitability for the study, to give you the opportunity to ask questions about the study and to ask you to provide written consent for your participation in the study. We ask that you attend this session fasted from midnight, although you may drink water freely. This visit will last approximately 45-min and will include:

i. a small blood sample to measure health parameters, including liver and kidney function
ii. a medical history discussion
iii. measures of your height and weight
iv. an assessment of your heart, including an electrocardiogram (ECG) to monitor your heart and a blood pressure check

Baseline Study Day

Once we have the received the results of your blood tests and on the premise that all of your results are within normal range, we will enrol you on to the study.

Before your first study visit, you will be asked to complete a diet diary for 4-days (including one weekend day) detailing what you ate and drank during those days. On your first study day we will ask you to attend the laboratory fasted at approximately 9am to have ultrasound measurements of your right leg to look at your muscle structure. An ultrasound machine uses soundwaves which humans cannot hear and provides information about structure underneath the skin (it does not use x-rays or any other form of radiation).

After this we will begin measurements of muscle and nerve function. To do this, we will assess levels of electrical activity in your muscle during movement. We will do this using electrodes placed on the surface of your skin, and also using a small pin-type electrode inserted into your muscle. We will also assess how well you can control the muscle by asking you to follow a force trace line on a monitor in front of you. This would be followed by assessments of physical function, such as balance and power.

Training Sessions

Your motor control training will take place 3 times each week for 4-weeks, and will be fully-supervised by a member of the research team. Each training session will last approximately 20- minutes. During these training sessions you will be asked to follow a force trace line, through contraction of your muscles, on the monitor in front of you which would vary in intensity throughout each session.

Reassessment Study Day

After the motor control training period, you will be asked to return for another visit where your baseline study day will be repeated.

Finally, we will ask you to complete two brief questionnaires about your thoughts on the training programme and the study you have completed.

What do I have to do?

We are studying the effects of motor control training on motor control. With the exceptions outlined above, we ask that you maintain your diet and physical activity levels as normal for the duration of the study.

What is the drug or procedure that is being tested?

This study assesses the effects of 4-weeks motor control training on muscle function parameters. No other drug or procedure is being tested.

What are the side-effects or risk of any treatment or procedures received when taking part?

Research studies often involve some risks, not all of which may be currently known. Blood tests can result in bruising around the area where the needle has been, although this procedure will only be performed by individuals trained and experienced in this technique. The pin-type electrode may prove uncomfortable for some, but the needle used is smaller than those used for routine blood samples and the procedure will only be performed by individuals trained and experienced in this technique.

What are the possible benefits of taking part?

We cannot promise the study will help you directly, but you may see improvements in your muscle function. Participation in the study will also provide you with some information about your muscle structure from the ultrasound scans. Overall it is hoped that the information we gain from this study will give us a better understanding of the effect of motor control training on muscle function parameters in both young and older adults. This information may help us design better guidelines for exercise training programmes, specifically in older adults, which enhance the ability to perform activities of daily living.

What are the possible disadvantages and risks of taking part?

Healthy volunteers have been chosen for this study; however, it is possible that the routine tests could detect unknown health problems. Examples of these include diabetes and high blood pressure, as they are common and often undiagnosed. Should this be the case, you will be informed and advised to attend your GP practice for further management. Your GP will also be notified.

What are the exclusion criteria for this study?

For this study we are recruiting healthy volunteers aged between 18 and 35 years and over 65 years, who are of normal weight or slightly overweight. If you have been a subject in any other research study in the last three months which involved: taking a drug, being paid an inconvenience allowance or having an invasive procedure (e.g. blood sample >50ml), you would not be eligible to take part.

You would also be unsuitable if you have particular medical conditions (such as neurological conditions) or are taking certain medications. If you are interested in this study, please discuss these further with the research team.

What if something goes wrong?

If you suffer any symptoms or side effects, you should report them immediately to the study research team (see end of sheet for contact details). If you have a concern about any aspect of this study, you should ask to speak to the study team who will do their best to answer your questions. The researchers contact details are given at the end of this information sheet. If you have a complaint on your treatment by a member of staff or anything to do with the study, you can initially approach the lead investigators Dr Beth Phillips or Dr Mathew Piasecki. If this achieves no satisfactory outcome, you should then contact the Ethics Committee Secretary, Mrs Louise Sabir, University of Nottingham, Faculty of Medicine & Health Sciences Research Ethics Committee c/o School of Medicine Education Centre, B Floor, Medical School, QMC Campus, Nottingham University Hospitals, NG7 2UH. E-mail: louise.sabir@nottingham.ac.uk .

Will my taking part in this study be kept confidential?

We respect your right to privacy, and we will take measures to safeguard confidentiality. A single form, on which you are asked to sign to give consent for involvement will carry details of your name and address, but no health-related details. This is kept securely in a locked cabinet within the Medical School. Access to this cabinet is restricted to personnel directly involved in the study and to University staff with direct responsibility for ensuring the study is conducted appropriately.

We will follow current ethical and legal practice and all information about you will be handled in confidence. If you join the study, some parts of the data collected about you will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by people authorised to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept strictly confidential, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the study site will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.

Your personal data (address, telephone number) will be kept for 5 years after the end of the study so that we are able to contact you about the

findings of the study and possible follow-up studies (if you agree to this). All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality and only direct members of the research team will have access to your personal data.

You can find out more about how we use your information and read our privacy notice at:

https://www.nottingham.ac.uk/utilities/privacy.aspx

What will happen to any samples I give?

We will seek your consent for any samples remaining after analysis for this study has been completed, to be stored and used in future research. This is optional and you will be asked to give separate consent for this. The samples will be securely stored with a code unique to you at the University of Nottingham under the Universities Human Tissue Research Licence (No. 12265).

Some of these future studies may be carried out by researchers other than the current research team. This may include researchers working for commercial companies. Any samples or data used will be anonymised so that you could not be identified in any way. If you do not agree to this, any remaining samples will be disposed of in accordance with the Human Tissue Authorities code of practice.

Will any genetic tests be done?

In the current study we will not be using your samples for genetic testing.

What will happen to the results of the research study?

Data collected during the study will be published in the scientific literature enabling other health professionals to use the information, it may also form part of an education thesis. You will not be identified in any publication. There is usually a delay of up to one year from the study completion before this occurs. Should you wish to be informed of publications resulting from this study, please inform the study team.

Who is funding the research?

This study is funded by the University of Nottingham and the Nottingham Biomedical Research Centre.

Who has reviewed the study?

This study has been reviewed and approved by the University of Nottingham Faculty of Medicine and Health Sciences Research Ethics Committee.

Contact for Further Information

Thank you for your interest in this study. For further information please contact: Miss Isabel Ely by email isabel.ely@nottingham.ac.uk or on 01332 724676. The research team is alternatively contactable at The University of Nottingham, Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, Royal Derby Hospital, Derby, DE22 3DT.

Appendix 1.2. Blank healthy volunteer consent form

Division of Medical Sciences and GEM, School of Medicine

University of Nottingham
UK | CHINA | MALAYSIA

Healthy Volunteer Consent Form (HVCF)

Premises covered	MSGEM	This is version	8
Document Created	15.7.2009	Document issued in	June 19
Review Period	Every two years	To be reviewed in	June 21

Project Title: Investigating age-related differences in motor control and neuromuscular parameters in response to motor control training.

Investigators: Dr Beth Phillips, Dr Mathew Piasecki, Miss Isabel Ely

REC REF: C16122016

Please read this form and sign it once the investigator above-named, or their designated representative, has explained fully the aims and procedures of the study to you.

	Please Initial Box
• I voluntarily agree to take part in this study.	☐
• I confirm that I have been given a full explanation of the study and that I have read and understand the information sheet (version number 8.1 dated 11/11/2019) for the above study and have had the opportunity to ask questions.	☐
• I understand that I am free to withdraw from the study at any time, without having to give a reason for withdrawing.	☐
• I agree to comply with the reasonable instructions of the research team and will notify them immediately of any unexpected unusual symptoms or deterioration of health.	☐
• I give permission to collect, store, analyse and publish information obtained from my participation in this study. I understand my personal details will be kept confidential.	☐
• I understand that data collected in the study may be looked at by responsible individuals from the University of Nottingham and regulatory authorities where it is relevant to my taking part in this study.	☐
• I understand that information about me recorded during the study will be kept in a secure database. If data is transferred to others it will be made anonymous. Data will be kept for 7 years after all results of this study have been published. After this time, it will be disposed of in line with University policy.	☐

- I understand that the tests or procedures are carried out for research only and not for clinical diagnostic purposes. However, if the study investigator should feel it necessary to inform my GP of my participation in the study, or of an adverse event or abnormal test result, I understand I am giving my consent to do so. ☐
- I confirm that I have disclosed relevant medical information before the study. ☐
- I have not been a volunteer in any other research study in the *last three months*, which involved: taking a drug, being paid an inconvenience allowance, having an invasive procedure (e.g. venepuncture >50ml, endoscopy) or exposure to ionising radiation. ☐
- I confirm that I have not been exposed to more than 5 mSv of ionising radiation in the *last 12 months* (to clarify, please discuss with a member of the research team). ☐

Healthy Volunteer Consent Form (HVCF)
Human Tissue Act:

OPTIONAL - I agree to my tissue/ blood samples being shared with other researchers including those working outside the University. I understand that I would not gain commercially. ☐

OPTIONAL - Where tissue is removed from my body for the purposes of this study, but not used for this study, and when the ethical approval for this project expires, I agree to the future and continued storage and use of this tissue for future research into functioning of the human body and disease. Such tissue will fall under the University of Nottingham licence of the Human Tissue Act. As specified under the Licence tissue records will be maintained for 25 years. ☐

Personal Data:

OPTIONAL - I agree to my contact details being stored for the purpose of being invited to participate in future research studies. ☐

Volunteer Name:
……

Signature: …… Date:
……..……..

I confirm that I (investigator) have fully explained the purpose of the study and what is involved to:

……
……..

I have given the above named a copy of this form together with the information sheet.

Investigator Name:
…….

Signature: ……. Date:
……..……..

PI Signature: …….. Date:
……

Study Volunteer Number:
……

2 copies: 1 for the participant, 1 for the study file.