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Interventions to improve neuromuscular function in older adults

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Abstract

Background:

Ageing is accompanied by a decrease in neuromuscular function that contributes to reduced independence, increased fall risk, and diminished quality of life. Sarcopenia and dynapenia, age-related losses in muscle mass and strength, are well documented, but growing evidence highlights the central role of impaired motor unit (MU) behaviour in functional decline. Of particular importance, reductions in MU discharge rates and increased discharge variability may impair force steadiness and control. Similar neuromuscular deficits are observed in stroke survivors, who often exhibit bilateral impairments despite unilateral brain lesions. Traditional resistance exercise training (RET) improves muscle strength but may be unsuitable for frail or mobility-limited individuals. There is a growing need for alternative, low-load, neural-targeted interventions that enhance neuromuscular control without imposing high mechanical stress.

Aims:

This thesis aimed to explore the neural mechanisms underpinning neuromuscular decline in ageing and stroke and to evaluate the efficacy of low-load interventions targeting neural function. The specific objectives of the thesis were: (i) to systematically review the evidence for cross-education (CE) effects following lower-limb unilateral RET and quantify contralateral strength gains in untrained limbs; (ii) to determine the neuromuscular adaptations induced by unilateral force accuracy training (FAT) in the vastus lateralis (VL) and tibialis anterior (TA) muscles of healthy older adults, using high-density surface EMG (HDsEMG) to track MU behaviour; (iii) to evaluate the extent of CE and the retention of neural adaptations following FAT; and (iv) to

characterise bilateral motor unit asymmetries in stroke survivors compared to age-matched healthy controls using identical HDsEMG protocols.

Methods:

A systematic review and meta-analysis was conducted to examine CE outcomes from unilateral lower-limb RET across published studies. For the experimental work, healthy older adults (aged 65–85) completed a 4-week unilateral FAT intervention targeting either the VL or TA. Neuromuscular function, including MU discharge characteristics, force steadiness, tracking accuracy, and strength, was assessed pre- and post-intervention, and again after 2 and 4 weeks of detraining. In a separate cohort, stroke survivors and age-matched controls underwent neuromuscular assessments to characterise MU behaviour and bilateral asymmetries in proximal and distal muscles.

Results:

The systematic review confirmed that unilateral lower-limb RET induces significant CE-related strength gains in the untrained limb, with a pooled standardised mean difference of 0.48 (95 % CI 0.35–0.61; $p < 0.001$), particularly when higher intensities and eccentric contractions were used. FAT in older adults increased maximal voluntary contraction by 10–15 % in the trained limb and 5–7 % in the untrained limb, accompanied by a 20–30 % reduction in force variability and a ~15 % decrease in motor-unit discharge variability, indicating a neural basis for CE. Certain neuromuscular adaptations persisted after two to four weeks of detraining. FAT affected proximal and distal muscles differently strength improvements were greater in the vastus lateralis, whereas precision and steadiness gains were larger in the tibialis anterior underscoring the relevance of muscle-specific evaluation. In stroke survivors, HDsEMG identified altered motor-unit discharge behaviour in both affected and unaffected limbs, characterised by lower recruitment efficiency (−20 to −45 % MVC)

and higher firing-rate variability ($p < 0.01$) relative to healthy controls, confirming bilateral neural impairment.**Conclusion:** This thesis demonstrates that low-load, neural-targeted interventions such as FAT can improve MU behaviour, force control, and induce CE effects in older adults. These adaptations are partly retained over time and may offer a feasible alternative to traditional RET. Furthermore, the characterisation of bilateral neuromuscular impairments in stroke survivors provides new insights into shared and distinct mechanisms of decline across ageing and clinical populations. The findings support the use of HDsEMG as a sensitive tool for monitoring neural adaptations and suggest that combining FAT and CE may be a promising strategy for rehabilitation in populations where high-load training is impractical.

Publications

Gamage, N.N., **Altheyab, A.,** Guo, Y., Phillips, B.E., Opie, G.M., Semmler, J.G., Atherton, P. and Piasecki, M., 2025. Bilateral neuromuscular adaptation to acute unilateral resistance exercise in healthy older adults. *GeroScience*, pp.1-17.

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Declaration

The data in this thesis was collected and analysed by myself unless otherwise acknowledged.

I declare that this thesis has been constructed by myself and that all the data presented are my own work unless otherwise stated. All published literature within this thesis has been appropriately referenced. None of the data presented in this thesis has been submitted towards the assessment of a higher degree previously.

Abdulmajeed Saad Altheyab

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List of Abbreviations

1-RM	1-Repetition Maximum
4MWT	4 Meters Walk Test
5xSTS	5 Times Sit to Stand
ADF	Ankle Dorsiflexors
ADL	Activity of Daily Living
AP	Action Potential
AUC	Area Under the Curve
BMI	Body Mass Index
CC	Correlation Coefficient
CE	Cross-education
CI	Confidence Interval
CIMT	Constant Induced Movement Therapy
CNS	Central Nervous System
COP	Centre of Pressure
CoV	Coefficient of Variation
CRF	Cardiorespiratory Fitness
CSA	Cross-sectional Area
CVA	Cerebrovascular Accidents
DR	Discharge Rate
ECG	Electrocardiogram
EMG	Electromyography
EMMs	Estimated Marginal Means
FAT	Force Accuracy Training

fMRI	Functional Magnetic Resonance Imaging
FMA	Fugl-Meyer Assessment
FS	Force Steadiness
FTA	Force Tracking Accuracy of Sinusoidal Task
GP	General Practitioner
GPT	Grooved Pegboard Test
HDsEMG	High-density Electromyography
HIIT	High-Intensity Interval Training
ICD	International Classification of Diseases
IRB	Institutional Review Board
ICH	Intracerebral Haemorrhage
iEMG	Intramuscular Electromyography
ISI	Inter-Spike-Interval
KE	Knee Extensors
LMM	Liner Mixed Effect Model
M1	Primary Motor Cortex
MD	Mean Difference
MU	Motor Unit
MUDR	Motor Unit Discharge Rate
MVC	Maximum Voluntary Contraction
NMES	Neuromuscular Electrical Stimulation
NMJ	Neuromuscular Junction
PIS	Participant Information Sheet
PNR	Pulse Noise Ratio

RCTs	Randomised Controlled Trials
RET	Resistance Exercise Training
SD	Standard Deviation
sEMG	Surface Electromyography
SMD	Standardised Mean Difference
TA	Tibialis Anterior
TMS	Transcranial Magnetic Stimulation
TUG	Timed Up and Go test
VL	Vastus Lateralis
WHO	World Health Organisation

Chapter 1: General introduction

1.1 Ageing population and neuromuscular decline

The age of the global population is increasing, presenting significant challenges for healthcare systems and societies across the world. In 2019, around 703 million people were aged 65 or older, a number expected to rise to 1.5 billion by 2050 (United Nations, 2020). This demographic shift is mainly due to falling birth rates and increased life expectancy. However, while people are living longer, they are not necessarily enjoying better health during those extra years. The idea of "healthspan", the time spent in good health, has not kept pace with overall lifespan. As a result, many individuals face extended periods of poor health later in life (Beard et al., 2016, Fries et al., 2011). In the UK, for example, healthy life expectancy is about 63 years for men and 64 for women, despite average lifespans now exceeding 80 years (ONS, 2021). This gap means that many older adults live nearly two decades with physical limitations, often linked to age-related declines in neuromuscular function.

Among the age-related health issues, neuromuscular decline is a major contributor to disability and loss of independence in older adults (Cruz-Jentoft et al., 2019b). Ageing is associated with reductions in skeletal muscle mass, strength, and power, collectively termed sarcopenia and dynapenia. Sarcopenia, as defined by the International Classification of Diseases, 10th Revision (ICD-10; code M62.84), describes the progressive and generalised loss of skeletal muscle mass and function with age (WHO, 1992), while dynapenia refers specifically to the loss of muscle strength that is not fully explained by atrophy (Clark and Manini, 2008). Muscle strength declines more rapidly than muscle mass, with estimates suggesting that adults lose approximately 1–2% of strength per year after the age of 50, leading to a cumulative reduction of up to 50% by the eighth or ninth decade of life (Goodpaster et al., 2006, Mitchell et al., 2012b).

The consequences of neuromuscular decline are profound. Reductions in muscle strength and function increase the risk of falls, frailty, and loss of mobility, with up to one-third of adults over 65 experiencing at least one fall per year (Rubenstein, 2006). Falls often result in fractures, hospitalisation, and loss of independence, and they represent a significant financial burden on healthcare systems (Pinedo-Villanueva et al., 2019). Furthermore, impaired muscle function is associated with metabolic disorders, including insulin resistance and type 2 diabetes, highlighting the systemic impact of age-related neuromuscular deterioration (Fielding et al., 2011).

Traditionally, sarcopenia research focused on muscular atrophy as the primary driver of functional decline. However, there is now substantial evidence that neural impairments, particularly those involving motor unit (MU) function, play a crucial role in the age-related decline in muscle function (Pabla et al., 2024, Piasecki et al., 2018). Neuromuscular ageing involves structural and functional deterioration in both central and peripheral nervous system components, manifesting in altered MU recruitment, lower discharge rates (DR), and greater discharge variability (Enoka and Farina, 2021). These changes may reduce force steadiness (FS) and compromise fine motor control, both of which are essential for safe ambulation, balance, and daily activities (Christou, 2011).

Importantly, the neuromuscular system exhibits sex-specific ageing trajectories. Females typically demonstrate lower absolute muscle mass and strength but often exhibit greater fatigue resistance and enhanced neuromuscular control during repetitive or submaximal tasks. This improved control has been linked to lower motor unit discharge rate (MUDR) variability and reduced force fluctuations during sustained contractions, which can be quantified using high-density surface electromyography (HDsEMG) and measures of FS (Hunter, 2014, Enoka and Farina, 2021). These

differences are partly attributed to variations in muscle fibre-type composition, hormonal milieu, and neural activation strategies (Haizlip et al., 2015). However, despite these observations, the majority of neuromuscular ageing studies have focused predominantly on male participants, leading to significant knowledge gaps regarding sex differences in neural adaptations and their functional implications (Guo et al., 2025). Emerging evidence suggests that the degree of neuromuscular decline may also vary between proximal and distal muscles. Proximal muscles, such as the quadriceps, are more susceptible to age-related atrophy and MU loss, whereas distal muscles, like the tibialis anterior, may be relatively spared due to their frequent activation in locomotor activities (Maden-Wilkinson et al., 2014). However, even distal muscles exhibit impaired neural modulation with advancing age, including increased MUDR variability and reduced recruitment efficiency (Piasecki et al., 2016a). Understanding these muscle-specific differences in neuromuscular ageing is critical for developing targeted interventions to preserve function in older adults.

As the proportion of older adults in the population continues to rise, maintaining neuromuscular health has become a public health priority. Strategies to counteract sarcopenia and dynapenia must consider both muscular and neural contributions to functional decline. While resistance exercise training (RET) has long been considered the gold standard intervention, there is growing interest in alternative approaches that specifically target neural mechanisms underlying force control and MU behaviour.

The following sections will explore the neural basis of age-related functional impairments and the potential of novel interventions, such as Force Accuracy Training (FAT) and cross-education (CE), to enhance neuromuscular performance in ageing and clinical populations.

1.2 Neuromuscular ageing

Age-related declines in muscle strength and function have traditionally been attributed to the progressive loss of skeletal muscle mass. However, recent advances in neurophysiology have highlighted that changes in the nervous system play a pivotal role in mediating neuromuscular decline. These neural factors include alterations in MU behaviour, impaired voluntary activation, and reduced coordination, which together compromise the ability to generate and control force effectively (Jones et al., 2022, Enoka and Farina, 2021).

The MU is the fundamental functional component of the neuromuscular system, consisting of a single alpha motor neuron and all the muscle fibres it innervates (Heckman and Enoka, 2012). Muscle force is regulated by the number of recruited MUs and the frequency of their action potentials, a process known as rate coding (Farina et al., 2014). The MUDR refers to the number of action potentials (per second, Hz) by a motor neuron, and it plays a critical role in modulating muscle force during both static and dynamic tasks. DR variability, typically quantified as the coefficient of variation of interspike intervals, reflects inconsistencies in neural output and is closely associated with reduced FS, particularly in older adults (Laine et al., 2015, Castronovo et al., 2015). Understanding these mechanisms is essential for developing targeted interventions aimed at preserving or restoring functional capacity in older adults.

1.2.1 Neural changes with age

At the spinal level, ageing is associated with a significant loss of alpha motor neurons. Histological studies suggest that up to 50% of motor neurons innervating limb muscles may be lost by the eighth decade of life (Tomlinson and Irving, 1977). This neuronal loss leads to the denervation of muscle fibres and a reduction in the number of functional MUs. Surviving motor neurons compensate through collateral sprouting, reinnervating orphaned muscle fibres to form larger but fewer MUs (Piasecki et al., 2016b). While

this reinnervation process helps preserve muscle mass, it leads to increased MU size and heterogeneity, which can impair the precision of muscle contractions.

Older adults often exhibit reduced maximal MUDRs during voluntary contractions, limiting their ability to generate rapid and powerful movements (Klass et al., 2008). In addition, there is increased variability in MU discharge patterns, which manifests as impaired FS, the ability to maintain a consistent level of muscle force during isometric contractions (Enoka and Farina, 2021). Force steadiness (FS) is critical for performing daily tasks such as holding objects, rising from a chair, or walking without tripping.

At the cortical level, age-related changes include reduced corticospinal excitability and alterations in intracortical inhibition and facilitation (Kamen et al., 1995, McGinley et al., 2010). These adaptations may contribute to impaired motor planning and execution, further exacerbating deficits in voluntary activation and coordination.

1.2.2 Functional implications

The functional consequences of these neural changes are profound. Increased variability in force output has been linked to reduced gait speed, impaired balance, and higher fall risk in older adults (Christou, 2011). Importantly, these deficits in neuromuscular control can occur independently of significant muscle atrophy, suggesting that interventions targeting neural mechanisms may be particularly effective for improving function in ageing populations (Galganski et al., 1993, Tracy et al., 2005b).

1.2.3 Insights from High-density surface electromyography

High-density surface electromyography (HDsEMG) has emerged as a powerful tool for studying MU behaviour in vivo. HDsEMG enables the non-invasive decomposition of surface EMG signals into individual MU action potential trains, providing detailed insights into recruitment strategies, DRs, and discharge variability (Farina et al., 2010). This technology has revealed age-related increases in MU discharge variability and a

lowering in recruitment threshold during submaximal contractions, offering mechanistic explanations for impaired FS in older adults (Del Vecchio et al., 2020).

1.2.4 Targeting neural mechanisms

The recognition that neural changes play a critical role in age-related functional decline has important implications for intervention strategies. While RET is widely regarded as the gold standard for preserving muscle mass and strength in older adults, its effects on neural control are less well established. Furthermore, high-load RET may not be feasible for all older adults due to frailty, joint pain, or comorbidities (Moseng et al., 2020b).

This has led to growing interest in low-load, neural-targeted interventions such as FAT. FAT involves low-intensity, isometric sinusoidal contractions that require precise force modulation, thereby challenging the neural control systems without imposing excessive mechanical stress on the musculoskeletal system (Christou and Enoka, 2011b, Ely et al., 2022). Emerging evidence from studies in young adults suggests that FAT can improve FS and reduce MUDR variability (Ely et al., 2022). While these neural adaptations have not yet been extensively studied in older adults, they provide a rationale for investigating FAT as a strategy to enhance functional performance in ageing populations.

1.3 Interventions for neuromuscular health

The age-related decline in neuromuscular function represents a critical public health challenge, as it is a key determinant of physical independence, quality of life, and longevity in older adults (Cruz-Jentoft et al., 2019b). The ability to generate and control muscle force underpins essential daily activities (ADLs) such as standing, walking, and maintaining balance. Interventions to mitigate or reverse neuromuscular decline are

therefore of significant interest, particularly as the proportion of older adults in the global population continues to rise (United Nations, 2020).

1.3.1 Resistance exercise training

RET is widely regarded as the most effective intervention for combating sarcopenia and enhancing muscle strength and mass in older adults. RET involves the application of external loads to stimulate muscle hypertrophy and strength gains through both neural and muscular adaptations (Phillips et al., 2017b). In older adults, RET has been shown to increase cross-sectional muscle area (CSA), enhance maximal voluntary contraction (MVC), and improve functional outcomes such as gait speed and balance (Fiatarone et al., 1990, Hunter et al., 2016). These adaptations result from increased muscle protein synthesis, enhanced MU recruitment, and improvements in neuromuscular coordination (Frontera et al., 1988, Narici and Maffulli, 2010).

RET also induces specific adaptations in MU recruitment and DRs behaviour. Studies have reported lower recruitment thresholds and increased mean DRs following high-load resistance training (Del Vecchio et al., 2019, Elgueta-Cancino et al., 2022). These neural adaptations contribute to the rapid strength gains often observed in the early phases of RET, prior to significant hypertrophy.

1.3.1.1 Limitations of high-load RET

Despite its efficacy, traditional high-load RET has limitations when applied to frail or mobility-limited older populations. Older adults often exhibit anabolic resistance, a blunted muscle protein synthetic response to exercise and dietary protein intake (Breen and Phillips, 2011), which reduces the hypertrophic potential of RET compared to younger counterparts, particularly in those with chronic inflammation or comorbidities (Brook et al., 2015).

Furthermore, high mechanical loads may not be feasible for individuals with joint pain, osteoarthritis, cardiovascular disease, or other age-related health conditions. In addition

to these physical barriers, psychological factors such as fear of injury and low confidence in performing demanding exercises can also reduce adherence to high-load training programmes (Moseng et al., 2020b). Collectively, these challenges highlight the need for alternative exercise strategies that can stimulate neuromuscular adaptations without imposing excessive mechanical stress.

1.3.1.2 Low-load alternatives

In response to these limitations, there has been increasing interest in low-load resistance exercise and neural-targeted interventions as potential alternatives. Low-load RET performed to volitional fatigue can induce comparable hypertrophy and strength gains to high-load RET in healthy older adults, likely due to the recruitment of high-threshold MUs as fatigue accumulates (Mitchell et al., 2012b, Schoenfeld et al., 2015). However, the efficacy of low-load RET may still be constrained by anabolic resistance in more frail individuals (Brook et al., 2016).

Beyond hypertrophy, interventions targeting neural control mechanisms offer a promising avenue for improving functional performance. Fine motor control, FS, and coordination are heavily dependent on the nervous system's ability to recruit MUs appropriately and modulate their DRs (Enoka and Farina, 2021). Enhancing these neural properties may yield functional benefits even in the absence of substantial muscle hypertrophy, particularly for tasks requiring precision and stability.

1.3.2 Neural-focused alternatives

Novel approaches such as FAT and CE are designed to target neural pathways directly. FAT involves low-intensity, isometric sinusoidal contractions that require precise modulation of force output, thereby challenging and refining MU recruitment and discharge variability (Christou and Enoka, 2011b). FAT has shown promise in improving FS and motor control in older adults, with potential applications in

populations unable to perform high-load RET (Ely et al., 2022, Del Vecchio et al., 2019).

CE, on the other hand, leverages the nervous system's plasticity to induce strength and skill gains in the untrained contralateral limb following unilateral training. This phenomenon is mediated by cortical and spinal mechanisms and may be particularly relevant for older adults and stroke survivors with unilateral impairments (Lee and Carroll, 2007a, Calvert and Carson, 2022).

These neural-targeted interventions represent a paradigm shift from traditional hypertrophy-focused training toward approaches that prioritise motor control and neural plasticity. By addressing the neural contributions to age-related functional decline, such strategies have the potential to complement or, in some cases, substitute for RET in frail populations.

Given the growing evidence supporting the role of neural mechanisms in functional decline and rehabilitation, the following sections will explore CE and FAT in detail. Understanding the underlying mechanisms and potential applications of these interventions is critical for developing effective strategies to improve neuromuscular health in older adults and clinical populations.

1.4 Cross-education

CE refers to the phenomenon where unilateral training of one limb results in strength, skill, or functional improvements in the contralateral untrained limb. First described over a century ago (Scripture et al., 1894). CE has since been demonstrated across various populations, muscle groups, and training modalities. Although the majority of strength gains occur in the trained limb, contralateral improvements of 8–25% in

strength have been reported, depending on the training protocol and muscle group (Lee and Carroll, 2007a, Munn et al., 2005a, Green and Gabriel, 2018b). These gains are mediated primarily by neural adaptations rather than hypertrophic changes, making CE particularly relevant for populations with unilateral impairments, such as older adults and stroke survivors.

1.4.1 Mechanisms

CE is thought to arise from central nervous system adaptations at multiple levels, including cortical, subcortical, and spinal circuits. Two principal theories, the cross-activation model and the bilateral access model, have been proposed to explain the phenomenon (Carroll et al., 2006a).

1.4.1.1 Cross-activation model

The cross-activation model suggests that unilateral training results in simultaneous activation of motor networks in both hemispheres. This bilateral cortical activation strengthens neural pathways controlling both limbs, facilitating improvements in the untrained side. Evidence from functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) studies supports increased excitability and connectivity in the ipsilateral motor cortex during unilateral contractions (Farthing et al., 2011, Kidgell et al., 2015b).

1.4.1.2 Bilateral access model

The bilateral access model proposes that motor engrams (neural representations of movement) formed during training in one hemisphere are accessible by the contralateral hemisphere. This shared access allows learned motor patterns and strength adaptations to transfer to the untrained limb (Lee and Carroll, 2007a).

Other contributing mechanisms include reduced interhemispheric inhibition, increased corticospinal excitability, enhanced activity in supplementary motor areas, and potential

adaptations in the reticulospinal tract (Calvert and Carson, 2022). At the spinal level, changes in motoneuron excitability and presynaptic inhibition may also contribute to CE effects (Hendy and Lamon, 2017).

1.4.2 Evidence in healthy adults

Meta-analyses of CE studies have consistently reported significant contralateral strength gains following unilateral resistance training (Green and Gabriel, 2018b). These effects are observed in both upper and lower limbs and appear to be independent of muscle hypertrophy in the untrained side, underscoring the neural basis of CE.

The magnitude of effect varies between studies, with contralateral strength gains typically ranging from 5 to 25%. Larger effects are often reported in the upper limbs compared to the lower limbs, which may reflect differences in cortical representation and usage patterns (Manca et al., 2017b).

The training modality also appears to influence CE outcomes, as eccentric training tends to elicit greater contralateral effects than concentric or isometric training (Altheyab et al., 2024). This may be attributed to the higher cortical demands associated with eccentric contractions (Hortobágyi et al., 2011).

Additionally, training intensity and volume play essential roles, with higher-intensity unilateral training protocols generally producing more robust CE effects (Carroll et al., 2006a).

Importantly, CE has been demonstrated in both young and older adults, suggesting that the ageing nervous system retains some capacity for cross-limb transfer (Farthing and Zehr, 2014a). This finding has significant implications for rehabilitation strategies targeting frail older adults and clinical populations with unilateral impairments.

1.4.3 Evidence in older adults

Age-related declines in neuromuscular function raise questions about the efficacy of CE in older populations. Neural plasticity diminishes with age, and older adults often exhibit impaired interhemispheric communication and reduced corticospinal excitability (Seidler et al., 2010). Despite these challenges, several studies have demonstrated significant CE effects in older adults, albeit sometimes of smaller magnitude compared to younger cohorts (Barss et al., 2016).

TMS studies in older adults have shown reduced interhemispheric inhibition and increased corticospinal excitability following unilateral training, supporting the preservation of neural mechanisms underpinning CE (Hinder et al., 2011).

Functionally, CE may help maintain strength and motor control in the non-trained limb, contributing to improved balance and greater independence in ADLs (Paillard, 2020). These findings are particularly encouraging for the development of interventions aimed at frail older adults who may be unable to engage both limbs actively in training.

1.4.4 Clinical applications

The potential of CE extends beyond healthy ageing to clinical populations with unilateral impairments, such as stroke survivors, individuals with limb immobilisation, and patients recovering from orthopaedic surgery (Farthing and Zehr, 2014a).

In stroke rehabilitation, CE has been used to improve strength and motor control in the paretic limb by training the non-paretic limb. Meta-analyses suggest moderate improvements in upper limb function in stroke survivors following CE interventions (Smyth et al., 2023a).

Similarly, in orthopaedic applications, CE can mitigate disuse atrophy during limb immobilisation, such as after casting or surgery. Training the contralateral limb preserves neural drive and facilitates faster recovery once the immobilised limb is reintroduced to activity (Hendy et al., 2012).

In older adults with unilateral impairments, CE may maintain strength and prevent further decline in the non-trained limb, thereby reducing fall risk and promoting functional independence (Yadav and Singh, 2023).

In the context of ageing and stroke, CE offers a low-risk, non-invasive intervention to promote neural plasticity and maintain function in populations where direct training of both limbs is challenging. Its neural focus complements traditional resistance training by targeting cortical and spinal circuits involved in strength and motor control.

While CE leverages cross-limb neural connections, FAT focuses on refining MU recruitment and discharge patterns within a single limb. FAT may enhance FS and motor control through precise, low-intensity contractions, offering another avenue for improving neuromuscular health in older adults. Together, CE and FAT provide complementary strategies for targeting neural mechanisms underlying age-related functional decline.

The following section will examine FAT in detail, highlighting its novelty, mechanisms, and potential applications for older adults and stroke survivors.

1.5 Force Accuracy Training

FAT is an emerging low-load exercise modality designed to improve fine motor control, FS, and neuromuscular coordination. Unlike traditional RET, which primarily targets muscular hypertrophy and maximal strength, FAT emphasises neural adaptations by challenging the nervous system's ability to generate and sustain precise levels of muscle force. This neural focus positions FAT as a potentially powerful intervention for older adults and clinical populations where high-load training may not be feasible or desirable.

1.5.1 Rationale for ageing

As highlighted earlier, ageing is associated with profound changes in MU behaviour, including reduced maximal DRs and increased discharge variability (Jones et al., 2022, Piasecki et al., 2016b). These neural changes manifest as impaired FS, the ability to maintain a constant force during isometric contractions, and compromised coordination during functional tasks (Enoka and Farina, 2021). Even in the absence of significant muscle atrophy, these neural deficits, such as impaired MU activation, delayed reaction time, and reduced cortical control, substantially increase the risk of falls and mobility decline in older adults. These deficits compromise both neuromuscular coordination and executive function, leading to slower corrective responses and reduced balance stability. Evidence from neuropsychological and motor-control studies shows that deterioration in cortical processing and sensorimotor integration contributes directly to fall risk (Liu et al., 2014, Lord et al., 2003, Enoka and Farina, 2021).

FAT directly addresses these neural mechanisms by requiring individuals to perform low-intensity, sinusoidal isometric contractions with precise force modulation. The repeated practice of accurately tracking force targets engages cortical and spinal circuits involved in motor control, promoting adaptations that enhance discharge consistency (Ely et al., 2022, Del Vecchio et al., 2019).

1.5.2 Mechanisms of adaptation

The neural adaptations elicited by FAT are thought to involve several complementary mechanisms. FAT requires the coordinated activation of a broad spectrum of MUs, including higher-threshold MUs that may otherwise be less frequently engaged during daily activities in older adults (Piasecki et al., 2016b). This coordinated recruitment may improve the nervous system's ability to generate smooth and sustained force across a range of intensities. For example, Del Vecchio et al. (2019) demonstrated that after just four weeks of isometric strength training, there were significant increases in MUDRs

and a lowering of recruitment threshold, even before any measurable hypertrophy had occurred (Del Vecchio et al., 2019).

Precise force-tracking tasks practised during FAT can lead to reductions in MU discharge variability, improving the consistency of neural drive and enhancing FS during low-intensity isometric contractions (Ely et al., 2022). More recently, Lecce et al. (2025) demonstrated that six weeks of unilateral strength training of the biceps brachii (35–70% MVF) enhanced MU discharge characteristics, including reduced variability, in both the trained and untrained limbs (Lecce et al., 2025).

At the cortical level, FAT demands sustained attention, coordination, and motor planning, which can promote neuroplastic changes in the primary motor cortex (M1) and supplementary motor areas. Studies using brain imaging and TMS have consistently shown that motor tasks requiring precision and consistency can reshape cortical representations involved in voluntary control (Rogasch et al., 2009). More recently, Dai et al. (2021) demonstrated that motor practice combining forceful contractions with an explicit goal to maintain force level significantly increased corticospinal excitability, an effect consistent with M1 plasticity and attention-triggered modulation (Dai et al., 2021).

Finally, the requirement to match force output to visual or proprioceptive cues strengthens sensorimotor integration, a key component of balance and postural control (Christou and Enoka, 2011b). Recent evidence from McCracken et al. (2023) further supports this, showing that motor learning tasks requiring precise force modulation

based on proprioceptive and visual feedback lead to enhanced neural processing and improved integration of sensory and motor signals (McCracken et al., 2023).

1.5.3 Comparison with resistance training

While RET remains the gold standard for increasing muscle mass and strength, its neural benefits may be limited, particularly at low intensities. FAT, in contrast, specifically targets neural control, offering complementary adaptations to those elicited by RET. Combining these modalities may provide a comprehensive approach to preserving neuromuscular health in older adults.

1.5.3.1 Clinical applications

The neural focus of FAT makes it particularly relevant for clinical populations with impaired motor control, such as stroke survivors. Post-stroke individuals often exhibit increased MU discharge variability and impaired FS, even in the non-paretic limb (Beauchamp et al., 2023). FAT may offer a low-risk strategy to enhance neural control and promote bilateral functional improvements.

Furthermore, FAT can be integrated with CE principles by applying it unilaterally to the non-paretic limb in stroke survivors. This approach may harness both direct neural adaptations in the trained limb and contralateral benefits via interhemispheric transfer, providing a dual mechanism to improve paretic limb function.

1.5.3.2 Integration with Cross-education

Combining FAT and CE offers a novel paradigm for rehabilitation in populations where high-load, bilateral training is not feasible. FAT primarily improves motor control and MU behaviour through direct neural adaptations, enhancing the precision of force production and MU discharge consistency. In contrast, CE leverages cortical and spinal plasticity to promote improvements in the contralateral untrained limb, facilitating strength and motor control gains even without direct exercise. When applied together, these approaches have the potential to provide a potent stimulus for neural

reorganisation, supporting both local and systemic neuromuscular adaptations. This dual mechanism may be particularly advantageous for older adults and clinical populations, such as stroke survivors or individuals recovering from unilateral injuries, who often cannot tolerate traditional high-intensity, bilateral resistance exercise training.

The following section will explore how stroke exacerbates neuromuscular decline and examine the potential of FAT and CE to address bilateral impairments in this clinical context. A detailed understanding of the mechanisms of post-stroke neuromuscular dysfunction is essential for developing tailored rehabilitation strategies that can optimise recovery and functional independence.

1.6 Stroke and neuromuscular decline

Stroke is one of the leading causes of adult disability worldwide, affecting over 13 million people annually and resulting in long-term functional impairments in more than half of survivors (Feigin et al., 2017). While improvements in acute medical care have reduced mortality, stroke survivors often experience persistent motor deficits that severely limit independence and quality of life (Johnson et al., 2019). These deficits include weakness (hemiparesis), spasticity, impaired coordination, and reduced balance, all of which are underpinned by profound neuromuscular changes. In older adults, who constitute the majority of stroke patients, these impairments are superimposed on age-related neuromuscular decline, compounding functional losses and creating unique rehabilitation challenges.

1.6.1 Neuromuscular changes post stroke

The primary neurological consequence of stroke is damage to the corticospinal tract and associated motor pathways, disrupting voluntary activation of muscles in the

contralateral limb. Hemiparesis, characterised by weakness and impaired control of the affected side, occurs in approximately 80% of stroke survivors (Nakayama et al., 1994b).

At the muscular level, stroke leads to rapid atrophy, changes in fibre-type composition, and alterations in metabolic capacity in the paretic limb (Ryan et al., 2002). However, these peripheral changes are secondary to central neural impairments. Damage to upper motor neurons reduces corticospinal excitability, diminishing descending drive to spinal motor neurons and resulting in impaired voluntary activation and strength loss (Stinear et al., 2007). MU behaviour is also substantially altered, as HDsEMG studies have shown reductions in MU recruitment, decreases in maximal DRs, and increased discharge variability in the paretic limb (McNulty et al., 2014, Beauchamp et al., 2023). In addition, stroke frequently induces spasticity and motoneuron hyperexcitability, partly due to increased persistent inward currents (PICs), which contribute to involuntary muscle activity and heightened resistance to stretch (Goreau et al., 2024, Mesquita et al., 2024). A more detailed overview of stroke pathophysiology, neural impairment, and rehabilitation approaches is provided in Chapter 5, which focuses specifically on bilateral neuromuscular function in stroke survivors.

Collectively, these neural and muscular alterations manifest as reduced strength, impaired FS, and diminished functional performance in the affected limb.

1.6.2 Bilateral deficits post-stroke

Historically, stroke rehabilitation programmes primarily targeted the hemiparetic limb to restore function on the affected side (Belda-Lois et al., 2011). More recently, however, evidence has emerged for bilateral training and cross-education approaches that also address the ‘unaffected’ limb and the inter-hemispheric system (Hatem et al.,

2016). The so-called “non-paretic” limb frequently exhibits weakness, impaired motor control, and altered MU behaviour compared to age-matched healthy individuals (Hendy and Lamon, 2017, Li, 2017). Studies have shown that the non-paretic limb may exhibit a 20–30% reduction in strength relative to healthy controls (Harris-Love et al., 2011). In addition to strength loss, HDsEMG studies reveal that MUs in the non-paretic limb display increased discharge variability, which is indicative of widespread neural adaptations affecting bilateral neuromuscular control (Beauchamp et al., 2023). Functionally, these bilateral impairments contribute to asymmetrical movement patterns, reduced balance, and an increased risk of falls, further compounding functional limitations in stroke survivors (Weerdesteyn et al., 2008).

Collectively, this evidence underscores the importance of bilateral neuromuscular assessment and the consideration of both limbs in the design of post-stroke rehabilitation strategies.

1.6.3 Comparison with healthy ageing

Both stroke and ageing are associated with MU remodelling, reduced DRs, and increased force variability (Jones et al., 2022, Hu et al., 2016). However, the mechanisms and timelines of neuromuscular decline differ substantially between these conditions. Ageing leads to a gradual deterioration of neural and muscular function over decades, allowing partial compensatory adaptations to develop. In contrast, stroke produces an abrupt loss of neural inputs, which often overwhelms these compensatory mechanisms and results in a rapid and pronounced functional decline. Furthermore, whereas age-related neuromuscular changes tend to be bilaterally symmetric, stroke-induced impairments are typically asymmetric, although the non-paretic limb often demonstrates subclinical deficits as well (Schambra et al., 2019). Another key difference lies in neural plasticity: the ageing nervous system retains a degree of

adaptive capacity, whereas stroke survivors frequently exhibit maladaptive changes, including heightened interhemispheric inhibition, which can limit functional recovery (Murase et al., 2004). Understanding these distinctions is crucial for developing tailored rehabilitation strategies that address both the chronic, symmetric nature of age-related neuromuscular decline and the acute, asymmetric deficits observed after stroke.

1.6.4 Rehabilitation challenges

Traditional rehabilitation strategies, such as task-specific practice and high-intensity RET, have demonstrated benefits for strength and function post-stroke (Noguchi et al., 2025). However, implementing these approaches in frail older adults presents significant challenges. Many stroke survivors experience comorbidities, fatigue, and spasticity, which can limit their ability to engage in high-load bilateral training. In addition to these physical limitations, psychological and logistical barriers such as fear of falling, musculoskeletal pain, and difficulties attending structured exercise sessions frequently reduce adherence to conventional rehabilitation programmes (Miller et al., 2017).

These constraints highlight the need for alternative interventions that are low-risk, accessible, and capable of promoting meaningful neural and functional adaptations without imposing excessive mechanical or psychological burden on this vulnerable population.

1.6.5 Neural-targeted interventions

Neural-targeted interventions, such as FAT and CE, offer promising strategies to address bilateral neuromuscular impairments in stroke survivors. FAT involves low-intensity, precisely controlled isometric contractions that challenge the nervous system to produce accurate and consistent force outputs. By enhancing the consistency of MUDR and improving FS, FAT has the potential to refine neuromuscular control and

facilitate functional improvements in both limbs (Ely et al., 2022, Del Vecchio et al., 2019, Lecce et al., 2025). In contrast, CE exploits the neural connections between hemispheres to induce strength and skill gains in the untrained contralateral limb following unilateral training. Evidence suggests that these improvements occur through mechanisms such as interhemispheric facilitation, cortical reorganisation, and enhanced spinal excitability (Lee and Carroll, 2007a, Calvert and Carson, 2022), with meta-analyses reporting significant functional gains in the paretic upper limb of stroke survivors (Smyth et al., 2023a).

When combined, FAT and CE may provide a dual mechanism for promoting neuroplasticity: FAT enhances local motor control and MU behaviour in the trained limb, while CE facilitates cross-limb transfer of strength and coordination. Together, these interventions could offer a low-risk, accessible alternative to high-load, bilateral training, particularly for frail stroke survivors unable to tolerate conventional exercise. Investigating the effects of FAT and CE in both older adults and stroke survivors offers an opportunity to elucidate the underlying mechanisms of neural plasticity and inform the development of targeted rehabilitation strategies. Leveraging advanced techniques such as HDsEMG to characterise MU behaviour provides an additional mechanistic insight into how neural adaptations translate into functional improvements in ageing and clinical populations.

The following sections will identify key gaps in the current literature and outline the specific aims and structure of this thesis.

1.7 Gaps in knowledge and rationale

The preceding sections have outlined the significant neuromuscular challenges associated with ageing and stroke, as well as the potential of novel interventions, such as FAT and CE, to target these issues. While considerable progress has been made in understanding neuromuscular ageing and recovery post-stroke, key gaps in the literature remain. Addressing these gaps is critical to advancing rehabilitation science and improving functional outcomes in older adults and stroke survivors.

1.7.1 Gaps in neuromuscular ageing

Ageing has been extensively studied in the context of sarcopenia and muscle atrophy; however, the neural mechanisms underpinning age-related functional decline have received comparatively less attention. MU remodelling, including the loss of MUs and the compensatory reinnervation of orphaned fibres, has been recognised as a hallmark of neuromuscular ageing (Jones et al., 2022, Piasecki et al., 2016b). This remodelling is often accompanied by increased MU discharge variability, which compromises the precision of force production and contributes to functional limitations in older adults. Despite these observations, longitudinal studies tracking MU behaviour and its relationship to functional outcomes remain scarce, limiting our ability to map the progression of neural decline across the lifespan.

Another key knowledge gap lies in the limited understanding of the ageing nervous system's capacity for plasticity. While evidence suggests that targeted interventions can modulate MU behaviour, the degree to which the ageing neuromuscular system can adapt, particularly in response to low-load, neural-targeted training such as FAT, remains poorly defined. This uncertainty constrains the design of effective rehabilitation strategies aimed at improving FS, motor control, and functional independence.

Finally, it is unclear whether neural adaptations to ageing and training differ between proximal and distal muscles. Proximal muscles such as the quadriceps (e.g., vastus lateralis (VL)) appear to be more vulnerable to age-related atrophy and MU loss, whereas distal muscles like the tibialis anterior may be relatively spared due to their habitual activation during locomotor activities. However, the extent to which these anatomical and functional differences influence neural adaptations to interventions remains underexplored.

Collectively, these gaps highlight the need for research that integrates MU physiology, neural plasticity, and muscle-specific responses to develop targeted strategies addressing both the muscular and neural components of age-related functional decline.

1.7.2 Current intervention limits

RET remains the cornerstone intervention for mitigating age-related neuromuscular decline, as it effectively enhances muscle mass and strength in older adults. However, its efficacy is often limited in frail or mobility-restricted individuals due to comorbidities, joint pain, and reduced exercise tolerance. Furthermore, older adults exhibit anabolic resistance, a blunted muscle protein synthetic response to both exercise and dietary protein, which can attenuate the hypertrophic effects of traditional high-load RET (Moseng et al., 2020b). These limitations have driven interest in low-load alternatives such as FAT, which aim to improve neuromuscular control without imposing excessive mechanical stress.

Despite this, FAT remains in its infancy as an intervention for older adults. Only a handful of studies have investigated the effect of low-load accuracy training in ageing populations, and these are frequently limited by small sample sizes and short intervention durations. For example, Ranganathan et al. (2001) found that a simple skilled motor task involving ball rotation improved force steadiness and motor neuron

excitability in older adults following eight weeks of training (Ranganathan et al., 2001). Moreover, few have provided mechanistic insight into how FAT modifies neural function because the application of advanced techniques, such as HDsEMG, remains rare in this context. As highlighted in a recent review by Pethick et al. (2022), existing work on ageing and skeletal muscle force control has identified benefits of skill- or accuracy-based training but has also emphasised the lack of mechanistic studies using advanced neurophysiological tools (Pethick et al., 2022b). As a result, our understanding of the neural mechanisms by which FAT may enhance MU behaviour and force control in older adults is incomplete, highlighting the need for further mechanistic research.

1.7.3 Gaps in cross-education

CE offers a unique opportunity to enhance strength and motor control in an untrained limb, providing a valuable strategy for populations unable to engage both limbs in training, such as older adults and stroke survivors. Despite this potential, most CE studies have focused on young, healthy adults, leaving limited evidence in ageing populations where neural plasticity and interhemispheric communication may be reduced (Farthing and Zehr, 2014a). Moreover, the mechanisms underpinning CE in lower limb muscles, particularly those related to MU behaviour, corticospinal drive, and interhemispheric inhibition, remain poorly characterised, especially in individuals with unilateral impairments such as stroke. This gap is clinically important, given that lower limb function is critical for mobility, balance, and fall prevention in older adults. Finally, very few studies have investigated the combined application of CE with FAT, an approach that could provide complementary benefits by simultaneously targeting corticospinal plasticity and motor control. Understanding the mechanisms and efficacy

of CE, alone and in combination with FAT, is therefore essential for developing effective, low-risk neuromuscular interventions for ageing and clinical populations.

1.7.4 Stroke and bilateral impairments

Stroke research has traditionally focused on the paretic limb; however, emerging evidence demonstrates that neuromuscular impairments are frequently bilateral, with the so-called non-paretic limb also showing deficits in strength, motor control, and MU behaviour compared to healthy age-matched controls (Hendy and Lamon, 2017, Beauchamp et al., 2023, Hu et al., 2016). Despite this, significant gaps remain in our understanding of how neural adaptations in the non-paretic limb contribute to functional asymmetries and long-term disability. Furthermore, the potential for low-load, neural-targeted interventions such as FAT to improve MU behaviour and functional performance in stroke survivors is largely unexplored. A further limitation in the literature is the underutilisation of advanced neurophysiological tools, such as HDsEMG, which could provide detailed insights into MU adaptations in both the paretic and non-paretic limbs. Addressing these gaps is critical for designing targeted rehabilitation strategies that account for bilateral neuromuscular impairments following stroke.

1.7.5 Novelty of this thesis

This thesis addresses critical gaps in our understanding of neuromuscular ageing and post-stroke impairment by investigating the effects of unilateral FAT on MU function in healthy older adults and by characterising bilateral neuromuscular asymmetries in stroke survivors. Its novelty lies in the integration of several key elements into a single research programme. First, the thesis employs HDsEMG to longitudinally track individual MUs, providing mechanistic insights into recruitment strategies, discharge variability, and rate modulation that underpin neural plasticity in response to low-load,

neural-targeted training. Second, it examines muscle-specific responses to FAT by comparing adaptations in the VL, a proximal muscle, with those in the TA, a distal muscle, to determine whether muscle location influences neural and functional outcomes. Third, the work evaluates the extent to which unilateral FAT induces CE effects, enhancing strength and motor control in the untrained limb, and investigates the retention of these adaptations following periods of detraining, thereby informing the durability of neural improvements. Finally, this thesis uniquely applies identical HDsEMG assessment protocols to both healthy older adults and stroke survivors, enabling a direct comparison of MU behaviour, FS, and bilateral asymmetries. While FAT interventions were conducted exclusively in the healthy ageing cohort, the inclusion of stroke survivors provides essential context for understanding how age-related changes interact with unilateral neurological injury.

Collectively, these components position this thesis to advance knowledge of neural mechanisms underlying functional decline and to inform the development of low-load, precision-based rehabilitation strategies for populations at high risk of disability.

1.8 Thesis aims and structure

The preceding sections have highlighted the profound impact of ageing and stroke on neuromuscular function and the limitations of traditional RET in addressing the neural components of functional decline. Emerging interventions such as FAT and CE show promise for enhancing MU behaviour and improving force control in older adults, while also holding potential relevance for clinical populations such as stroke survivors. However, critical gaps remain in understanding the mechanisms underlying these interventions, their muscle-specific effects, and their broader applicability across

populations with different forms of neuromuscular impairment. To address these gaps, this thesis investigates the neuromuscular adaptations to FAT in healthy older adults using HDsEMG to provide detailed mechanistic insights into motor unit recruitment, discharge variability, and force control, alongside the potential for cross-education effects.

The primary aim of this thesis is to determine the neuromuscular adaptations elicited by low-load, neural-targeted FAT in healthy older adults and to evaluate their mechanistic relevance and potential clinical application, particularly with regard to MU behaviour and contralateral transfer of training effects. The research programme is structured around several interrelated objectives. First, it evaluates and quantifies the effects of unilateral lower limb RET on cross-education outcomes, including strength and functional gains in the untrained contralateral limb, through a systematic review and meta-analysis that has been published as Chapter 2. Second, it characterises the effects of unilateral FAT on general motor function, force steadiness, force-tracking accuracy, and motor unit discharge behaviour in both proximal (VL) and distal (TA) muscles of healthy older adults. Third, it investigates the extent to which unilateral FAT produces cross-education effects in the untrained limb and examines the retention of neural adaptations during detraining periods. In addition, this thesis explores bilateral neuromuscular characteristics in stroke survivors using the same HDsEMG protocols, allowing direct comparison with healthy older adults to define the extent of asymmetry and to contextualise age-related changes against post-stroke impairments. Finally, it considers the translational potential of FAT and CE as low-load, neural-targeted strategies that may promote neural plasticity and improve motor control in populations where conventional high-load interventions are not feasible.

The thesis is presented across six chapters. Chapter 1 provides a comprehensive general introduction, outlining the burden of neuromuscular ageing and stroke, the limitations of current interventions, and the rationale for investigating neural-targeted training strategies. Chapter 2 presents the published systematic review and meta-analysis examining the cross-education effects of unilateral lower limb RET. Chapters 3 and 4 report experimental studies investigating neuromuscular adaptations to unilateral FAT in the VL and TA, respectively, using HDsEMG to provide mechanistic insights into motor unit behaviour and cross-limb effects. Chapter 5 characterises bilateral neuromuscular asymmetries in stroke survivors and compares these to age-matched healthy older adults. Chapter 6 integrates the findings from all experimental studies, discusses the implications for rehabilitation strategies, and identifies directions for future research.

This thesis makes several key contributions to the field. It applies HDsEMG to longitudinally track motor unit adaptations in the ageing neuromuscular system, provides novel insights into the neural mechanisms underpinning FAT and CE, and evaluates the potential of low-load, neural-targeted training as a complementary or alternative approach to conventional RET. By advancing both mechanistic understanding and practical application, this work aims to inform the development of effective, accessible interventions that preserve neuromuscular function and support independence in older adults and clinical populations at risk of disability.

Chapter 2: Cross-education of lower limb muscle strength following resistance exercise training in males and females: A systematic review and meta-analysis

2.1 Abstract

Background: Cross-education describes the training of one limb which leads to performance enhancements in the contralateral untrained limb, driven by neural changes rather than muscle adaptation. In this systematic review and meta-analysis, we aimed to evaluate the efficacy of cross-education (versus a control group) via resistance exercise training (RET) for improving muscle strength in the untrained lower limb of healthy males and females.

Methods: A literature search from inception to September 2023 was conducted using MEDLINE (via PubMed), the Cochrane Library (CENTRAL), Web of Science (Core Database), Scopus, EBSCO-host, and Ovid-Embase. Independent screening, data extraction, and quality assessment were conducted. The measured outcomes were change in one-repetition maximum (1-RM) load, maximum voluntary contraction (MVC), and concentric, eccentric and isometric peak torque. Change in muscle structure (pennation angle and muscle thickness) was also analysed.

Results: A total of 29 studies were included. The pooled effect size from the random-effects model shows that cross-education significantly increased 1-RM compared to the control group (standardised mean difference (SMD): 0.59, 95% CI: 0.22 to 0.97; p=0.002). Cross-education also significantly improved MVC (SMD: 0.55, 95% CI: 0.16 to 0.94; p=0.006), concentric (SMD: 0.61, 95% CI: 0.39 to 0.84; p<0.00001), eccentric (SMD: 0.39, 95% CI: 0.13 to 0.64; p=0.003), and isometric (SMD: 0.45, 95% CI: 0.26 to 0.64; p<0.00001) peak torque, each compared to the control group. When resistance exercise training (RET) was categorised as eccentric or concentric, subgroup analysis showed that only eccentric training was associated with significantly increased

isometric peak torque via cross-education (SMD: 0.37, 95% CI: 0.13 to 0.61; p=0.003) (concentric, SMD: 0.33, 95% CI: -0.09 to 0.74; p=0.12).

Conclusions: This systematic review and meta-analysis emphasise the potency of cross-education for improving lower limb muscle strength. These findings have potential implications for clinical situations of impaired unilateral limb function (e.g., limb-casting or stroke). Future work exploring the mechanisms facilitating these enhancements will help to develop optimised rehabilitation protocols.

2.2 Introduction

The development and preservation of muscle function is not only pivotal for performing activities of daily living and recreation (Winett and Carpinelli, 2001), but also for recovery from situations of clinical stress (i.e., injury, illness, surgery). Exercise training, especially resistance exercise training (RET), has been shown to improve numerous aspects of both muscle structure (e.g., mass) and function across the life course, including strength (Westcott, 2012, Carvalho et al., 2022, Schoenfeld et al., 2016, Phillips et al., 2017a). These improvements in muscle function are dominated by changes in both the morphological characteristics of the muscle (e.g., fibre size, type distribution, and capillary density) and its neural activation (e.g., motor unit recruitment and firing rate) (Škarabot et al., 2021).

Unilateral RET has been shown to enhance strength and neural activation in the contralateral, non-exercised limb (Zhang et al., 2023), a process known as "cross-education", "cross-transfer" or "cross-training" (Fimland et al., 2009, Coratella et al., 2015). This cross-education is rarely associated with increased muscle mass or changes in muscle structure in the untrained muscles (Kurobe et al., 2015, Farthing et al., 2011), with neural adaptations purported to underlie this effect. Specifically, such changes may stem from simultaneous yet minor activation of the untrained hemisphere during

unilateral contractions, or the formation of motor engrams from unilateral training that are utilised during bilateral movements (Frazer et al., 2018, Farias et al., 2021, Ruddy and Carson, 2013). For instance, complex motor tasks have been shown to increase ipsilateral brain activity (Verstynen et al., 2005) and produce significant cross-education effects (Kidgell et al., 2017). Similarly, high-force muscle actions can also lead to increased ipsilateral brain activity (Andrushko et al., 2021) and potentiate cross-education (Urbin et al., 2015b). Eccentric muscle actions, characterized by decreased ipsilateral inhibition, have been found to produce robust cross-education outcomes (Kidgell et al., 2015a), increase brain activity (Fang et al., 2004, Canepa et al., 2021) and produce potent cross-education effects (Farthing and Chilibeck, 2003). These findings underscore the complexity of neural adaptations in response to unilateral training. Although several studies report observations of cross-education (Munn et al., 2005b, Carroll et al., 2006b, Maroto-Izquierdo et al., 2022, Mandal et al., 2023, Manca et al., 2015, Magdi et al., 2021, Lepley and Palmieri-Smith, 2014), some have suggested that observed increases in muscle function in the untrained limb may be due to familiarity with testing procedures or sub-optimal study design, including a lack of control groups, offering only within-group results (Munn et al., 2005b, Carroll et al., 2006b). In addition, several studies have shown that cross-education contralateral gains are only modest in magnitude, and perhaps not of substantial functional or clinical importance (Munn et al., 2005b, Manca et al., 2016b, Lexell and Downham, 2005). However, a recent meta-analysis of five studies showed that cross-education significantly improved upper limb function in patients after stroke, suggesting that it may be effective inducing improvements in motor control (Smyth et al., 2023b).

The research interest in cross-education is partly motivated by its clear potential in clinical applications (Farthing and Zehr, 2014b, Magnus et al., 2013, Manca et al.,

2016a, Manca et al., 2017a, Ehrensberger et al., 2016). Randomised controlled trials (RCTs) in healthy participants have reported larger contralateral strength gains in lower compared to upper limbs (Fimland et al., 2009, Latella et al., 2012, Lagerquist et al., 2006, Goodwill et al., 2012, Abazovc et al., 2015), and although mechanisms for this are unclear, it remains relevant for an ageing population where the majority of post-fall fractures occur in the hip (Parkkari et al., 1999). There is also a growing body of evidence suggesting that eccentric RET is the favourable modality (compared to concentric RET) to elicit contralateral strength gains (Lepley and Palmieri-Smith, 2014, Kidgell et al., 2011, Hortobgyi et al., 1999, Hortobgyi et al., 1997), a suggestion that is perhaps not surprising given the greater muscle damage and subsequent adaptation associated with eccentric RET (Proske and Morgan, 2001, Hody et al., 2019).

Several systematic reviews and meta-analyses have previously examined the cross-education effect, demonstrating that unilateral resistance training can increase contralateral strength through neural mechanisms (Manca et al., 2017b, Hendy and Lamon, 2017). These reviews collectively reported moderate overall effect sizes (SMD ≈ 0.4–0.6) and highlighted that eccentric contractions and longer training durations tend to produce greater transfer effects. However, most prior analyses have focused on upper-limb exercises, with limited evaluation of lower-limb training, ageing populations, and task-specific outcomes such as MVC versus concentric peak torque. Moreover, no study has quantitatively assessed whether training variables (e.g., intensity, contraction mode, or session frequency) systematically influence the magnitude of cross-education. The present review, therefore, aimed to synthesise and extend this literature by conducting a focused meta-analysis of lower-limb resistance exercise training, identifying the key moderators of strength transfer and assessing the evidence quality across studies

Given these developments, this review aims to systematically examine and assess the current literature on cross-education by RET compared to controls, focusing on the lower limbs of healthy individuals.

2.3 Methods

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021); and utilised the Cochrane Handbook for Systematic Reviews of Interventions to guide the conduct of this review (Cumpston et al., 2022). The study protocol was registered on PROSPERO (CRD42023458818), Appendix I.

2.3.1 Eligibility criteria and PICOS framework

We included studies based on the following criteria:

- Population (P): Healthy volunteer individuals of all ages and genders.
- Intervention (I): Unilateral resistance training of one lower limb intended to elicit cross-education in the untrained limb.
- Comparator (C): Studies were required to include a comparator or control group (e.g., non-training, contralateral training, or alternative intervention) to ensure methodological robustness and control for time or learning effects, even though data from the control group were not included in the meta-analytic model.
- Outcome (O): Strength change in the contralateral untrained limb, measured via maximal voluntary contraction, torque, or comparable indices.
- Study design (S): Randomised controlled trials (RCTs).

The inclusion criteria required that eligible studies incorporated a control or comparator group. This requirement was implemented to ensure that only studies with adequate methodological rigor and the ability to control for temporal or learning effects were

included in the review. Although the meta-analysis ultimately focused on within-study comparisons between trained and untrained limbs, the presence of a control group provided confidence that observed strength changes in the untrained limb were attributable to the intervention rather than measurement variability or external confounders. This decision was made to align with the Cochrane recommendations for reducing bias in training-based interventions (Higgins et al., 2019).

Studies where both limbs were simultaneously trained, where strength training was not the primary outcome and any studies of participants with specified clinical conditions were excluded.

2.3.1.1 Information source and search strategy

A literature search from inception to September 2023 was conducted using MEDLINE (via PubMed), the Cochrane Library (CENTRAL), Web of Science (Core Database), Scopus, EBSCO-host, and Ovid-Embase. The keywords used were "cross-education", "cross-transfer", "cross-training", "interlimb transfer", "strength transfer", "contralateral strength training", "unilateral strength training", "resistance training", "resistance exercise", "lifting", "weightlifting", "weight training", "strength training", and "power training". Supplementary Material 1 (Appendix I) shows the complete list of keywords used in each database. We conducted a comprehensive search identifying studies containing the specified keywords across all fields without imposing restrictions on document type, language, or availability of full text. We expanded our search criteria to include studies regardless of language and full-text access, ensuring a thorough and inclusive literature review. Additionally, we incorporated grey literature and utilised inter-library loans to access studies beyond our immediate electronic database resources. All identified studies were subjected to a rigorous peer review process to maintain the integrity of our research. Moreover, a comprehensive search of grey

literature databases, including HMIC, NTIS, OpenGrey, and PsycEXTRA, was conducted.

2.3.1.2 Study selection

Following the database searches, all citations were imported into EndNote X9 (Windows version). Duplicate references resulting from the overlap of database content were identified and removed. Two independent reviewers (AA and HA) screened the titles and abstracts of all unique citations against the pre-defined inclusion and exclusion criteria. Any disagreements between the two reviewers at this stage were resolved through discussion. Studies that appeared to meet the inclusion criteria but for which there was insufficient information in the title and abstract to make a clear decision advanced to full-text review. Again, two independent reviewers (AA and HA) assessed each full-text article to determine its eligibility. The reference lists of all included studies were scanned to identify any additional studies that may have been missed during the initial database searches. Any potentially relevant studies identified through this process were subjected to full-text review and included if they met the criteria.

2.3.1.3 Data collection

For studies that met the inclusion criteria, relevant data were extracted using a standardised data extraction form. This form was piloted on a subset of included studies and refined as required. Data was extracted regarding: i) study characteristics (study title, participant groups, country, study design, sample size, inclusion criteria, and main outcomes), ii) participant characteristics (age, sex, weight, height, body mass index), iii) intervention characteristics (type of RET, number of sessions, and repetition number), and iv) outcomes.

2.3.2 Risk of bias assessment

The risk of bias for included studies was independently assessed by two reviewers (AA and HA) using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2)

(Higgins et al., 2019). This tool evaluates five domains: i) bias arising from the randomisation process, ii) deviations from intended interventions, iii) missing outcome data, iv) outcome measurement, and v) selection of reported results. Each domain was categorised as having 'low risk', 'some concerns', or 'high risk' of bias based on specific signalling questions in the RoB 2. The overall risk of bias for each trial was then determined by the individual domain ratings. Discrepancies between the reviewers' assessments were resolved through discussion or consultation with a third reviewer as required.

2.3.3 Certainty assessment

In assessing the quality of evidence and the strength of recommendations, we employed the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology. The GRADE approach provides a systematic framework for rating the quality of evidence in systematic reviews and for grading the strength of recommendations in guidelines (Guyatt et al., 2008). This method categorises the quality of evidence into four levels: high, moderate, low, and very low, based on factors such as study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations. The results are presented in the Summary of Findings and GRADE Assessment table (Table 2.3)

2.3.4 Data synthesis

All statistics were conducted using Review Manager 5.4 (Windows version). We calculated the standardised mean difference (SMD) between both groups based on the inverse-variance model. Using the I^2 statistic, we calculated the percentage of heterogeneity and inconsistency between studies, with values of 25%, 50% and 75% deemed 'low', 'moderate' and 'high', respectively. We have employed a random-

effects model for all analyses. In studies that reported mean and standard error (SE) or 95% CI, the standard deviation (SD) was calculated using the following formulas:

$$SD = SE \times \sqrt{N}$$

$$SD = \sqrt{N} \times (\text{upper limit} - \text{lower limit}) / 3.92, \text{ respectively.}$$

Furthermore, for the studies that reported the baseline and post-intervention mean, we calculated the mean difference and SD for the mean difference by using the following formulas:

$$SD = \sqrt{PRE(SD^2)} + \sqrt{POST(SD^2)}.$$

Tau-square, chi-square, and I-square were reported. We performed a "leaving one out " sensitivity analysis by excluding the study causing heterogeneity (Patsopoulos et al., 2008). This involved recalculating the meta-analysis effect size multiple times, each time omitting a different single study. By systematically removing each study in turn, we were able to identify any particular study that, when excluded, resulted in a significant change in the overall effect size. This approach allowed us to determine the robustness of our findings and to pinpoint any studies that contributed disproportionately to heterogeneity. Moreover, subgroup analyses to explore potential sources of heterogeneity in cross-education (CE) strength outcomes, subgroup analyses were planned a priori based on two factors identified in previous literature as potential moderators of CE magnitude: type of resistance training and participant sex.

The type of training subgroup compared studies that used eccentric, concentric, or isometric unilateral resistance exercise, as contraction mode has been shown to differentially influence neural and strength adaptations (Manca et al., 2017b). The sex subgroup compared outcomes from studies involving male and female participants to explore possible sex-related differences in neural plasticity and strength transfer (Hendy and Lamon, 2017).

Other potential moderators, such as muscle group and age group, were considered but could not be examined due to an insufficient number of studies reporting these details. These gaps in the available data are noted as methodological limitations in the discussion.

2.4 Results

2.4.1 Literature search

A total of 1351 citations were identified from six databases. After excluding duplicates (n=733), a total of 618 citations were taken to the title and abstract screening. Of these articles, 573 citations were excluded as they did not meet the inclusion criteria. Full-text screening was conducted on 52 articles; of them, 23 were excluded, leaving 29 for inclusion in this systematic review and 20 studies included in the meta-analysis (Abazovc et al., 2015, Carolan and Cafarelli, 1992, Colomer-Poveda et al., 2021, Coratella et al., 2015, Coratella et al., 2022, Evetovich et al., 2001, Farias et al., 2023, Fimland et al., 2009, Garfinkel and Cafarelli, 1992, Goodwill et al., 2012, Hosseinzadeh et al., 2015, Hortobgyi et al., 1997, Hortobgyi et al., 1999, Kadri and No, 2017, Kannus et al., 1992, Kim et al., 2011, Lagerquist et al., 2006, Latella et al., 2012, Lepley and Palmieri-Smith, 2014, Manca et al., 2015, Mandal et al., 2023, Maroto-Izquierdo et al., 2022, Martnez et al., 2021, Mendonca and Vila, 2021, Razian et al., 2022, Shima et al., 2002b, Tøien et al., 2018, Weir et al., 1995, Weir et al., 1997) (**Figure 2.1**).

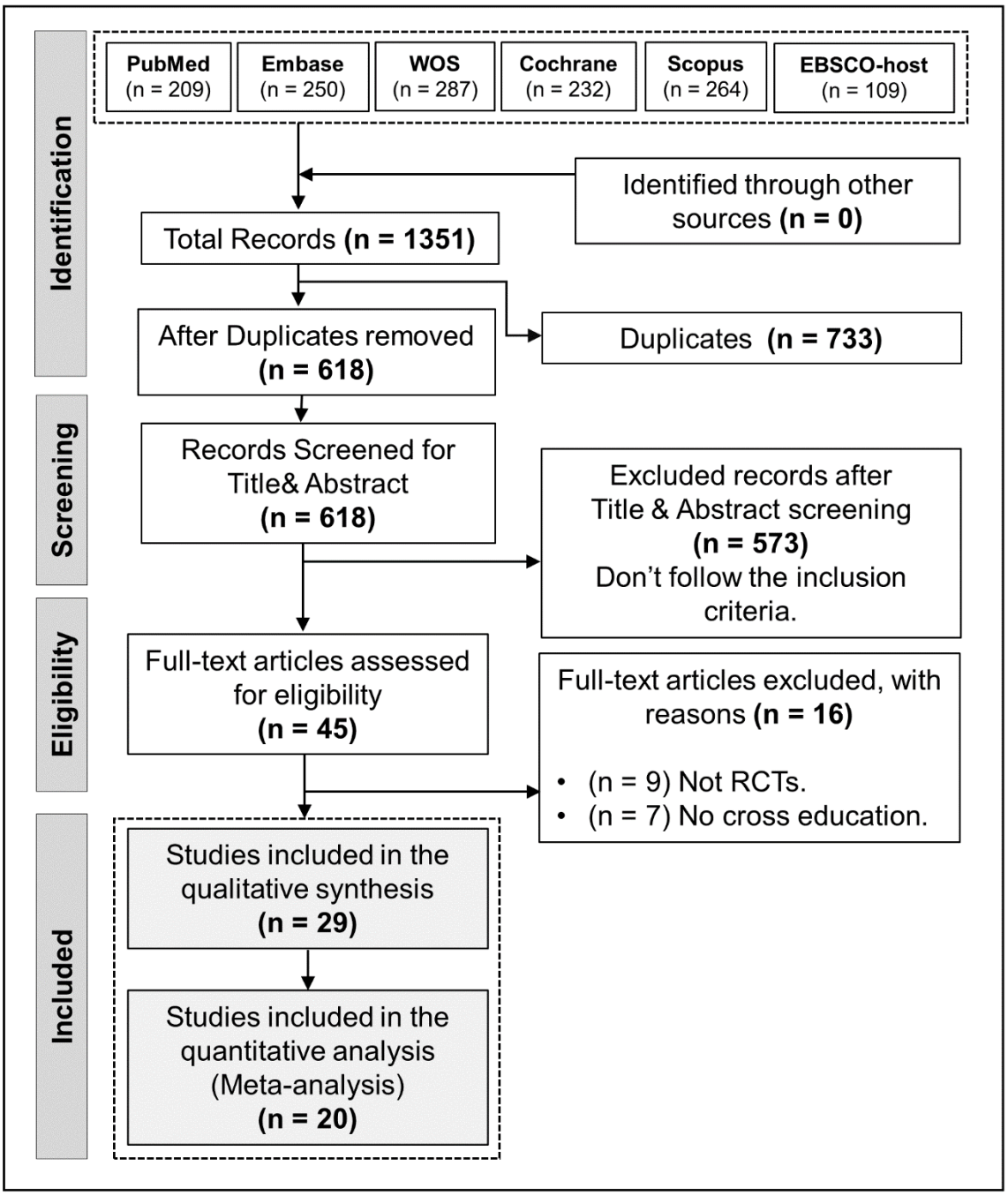


Figure 2.1:PRISMA flow diagram

2.4.1.1 Characteristics of Included Studies

A total of 29 RCTs were included, spanning from 1992 to 2023. The studies were conducted in various countries, with the distribution as follows: the US (n=7), Spain (n=4), Australia (n=3), Canada (n=3), Italy (n=3), Norway (n=2), Algeria (n=1), Bosnia and Herzegovina (n=1), Iran (n=1), Japan (n=1), Portugal (n=1), South Korea (n=1),

and the UK (n=1). The number of participants in these studies ranged from 14 to 60. The duration of the interventions varied widely, with the shortest being 2-weeks and the longest being 12-weeks. Most of the studies (68%) had participants training 2 or 3 times each week, although some did incorporate 4 or 5 sessions weekly. The type of exercise varied across the studies and included isokinetic knee extension and flexion, leg press, calf raises, leg extensions, isometric contractions, and other unilateral leg exercises. The common range of repetitions was between 3-6 sets of 5-12, although there were studies that prescribed more or less than this. Study details are shown in Table 2.1

2.4.1.2 Characteristics of included participants

The mean age of the participants varied across the studies. The majority of studies included younger adults, typically in their 20s, although some studies specifically focused on older adults in their 60s and 70s. Some studies had sex-specific cohorts (either all males or all females), while others included both sexes. On average, 56.3% of participants across the studies were male. Although BMI was not reported for all studies, from those that did, the average BMI ranged from 21 to 28 kg/m^2. Participant characteristics are detailed in Table 2.2.

Table 2.1: Summary of the included studies. RCT: randomised controlled trial, NR: not reported.

Study ID	Country	Study design	N	Intervention period	Number of sessions	Type of exercises	Repetition	Conclusion
Abazovic et al. 2015 (Abazovc et al., 2015)	Bosnia and Herzegovina	RCT	30	4 weeks	3 sessions a week	Unilateral nondominant (ND) isokinetic knee extension and flexion	2 to 4 sets of 5–6 repetitions	The cross-education exercises effect was not limited to the training speed, suggesting that utilizing a protocol involving multiple rates may not be necessary.
Carolan et al. 1992 (Carolan and Cafarelli, 1992)	Canada	RCT	20	8 weeks	3 sessions a week	Isometric extension maximal voluntary contractions	30 Contractions	They concluded that a minor yet meaningful reduction in hamstring coactivation observed during the initial training phases represents a non-hypertrophic adaptation of the neuromuscular system.
Colomer-Poveda et al. 2021 (Colomer-Poveda et al., 2021)	Spain	RCT	42	4 weeks	4 sessions a week	Unilateral knee extension RT with the dominant leg	5 to 6 repetitions	High-load resistance training, but not low-load resistance training, was found to enhance maximal voluntary force in both the trained and untrained knee extensors. Surprisingly, fatigue did not further enhance these improvements. Additionally, the upgrades in voluntary force were not associated with changes in corticospinal excitability (CSE) in either leg.
Coratella et al. 2015 (Coratella et al., 2015)	Italy	RCT	49	6 weeks	Twice a week	Unilateral isokinetic eccentric knee extensions and unilateral eccentric knee extensions on a knee-extension	5 sets of 8 repetitions	Eccentric training demonstrated effectiveness in inducing strength adaptations in the untrained limb, but it did not lead to structural changes. Utilising easily accessible gym devices could be a viable alternative to expensive and less accessible isokinetic devices in rehabilitation and training practices.

Coratella et al. 2022 (Coratella et al., 2022)	Italy	RCT	60	8 weeks	Twice a week	Unilateral dynamic constant external load knee extension training	5 sets of 6 to 7 repetitions	The results indicated that both eccentric (ECC) and traditional (TRAD) training led to increased strength in the contralateral knee extensors in all modes of contraction (concentric, eccentric, and isometric). However, concentric (CONC) training only resulted in increased concentric strength.
Evetovich et al. 2001 (Evetovich et al., 2001)	US	RCT	20	12 Weeks	3 sessions a week	Unilateral concentric-only isokinetic leg extension training of the nondominant limb	3 sets of 10 repetitions in the first week 4 sets in the second 5 sets in the third 6 sets from 4^{th} to 12^{th}.	The results of the EMG data indicated no significant change in EMG amplitude in the trained or untrained limb for the TRN or CTL group. An increase in peak torque PT over the 12 weeks in both the trained and untrained limb for the TRN group but no significant change in PT in either limb for the CTL group.
Fariñas et al. 2023 (Farias et al., 2023)	Spain	RCT	35	5 weeks	Twice a week	Traditional set configuration program with sets close to muscular failure	4 sets of 8 repetitions	These findings indicated that in situations where bilateral exercises were not feasible due to, for example, a leg injury, it was advisable to utilize traditional set configurations to enhance maximal voluntary force in the untrained leg.
Fimland et al. 2009 (Fimland et al., 2009)	Norway	RCT	26	4 weeks	4 sessions a week	Unilateral plantar flexion training of the dominant limb	6 sets of 6 repetitions	The study findings further supported the idea that increased neural drive to the contralateral agonist muscles played a crucial role in the cross-education of strength.
Garfinkel et al. 1992 (Garfinkel and Cafarelli, 1992)	Canada	RCT	15	8 weeks	3 sessions a week	Isometric resistance training of the knee	30 Contractions	There was no indication of non-hypertrophic changes resulting from resistance training of this specific type and intensity. Instead, the enhanced muscle strength appears to stem from creating additional contractile proteins through protein synthesis.

Goodwill et al. 2012 (Goodwill et al., 2012)	Australia	RCT	14	3 weeks	3 sessions a week	Single right leg squats	6 sets of 6-8 repetitions	The results showed that corticomotor adaptation occurs in response to unilateral leg strength training within the primary motor cortex (iM1).
Hosseinzadeh et al. 2015 (Hosseinzadeh et al., 2015)	Australia	RCT	26	-	-	high-intensity eccentric exercise of tibialis anterior	6 repetitions per set	Contralateral repeated bout effect was associated with spinal facilitation of the neuronal pathways situated at a homologous innervation level.
Hortobágyi et al. 1997 (Hortobgyi et al., 1997)	US	RCT	21	12 weeks	3 sessions a week	Isokinetic eccentric or concentric quadriceps strengthening	6 sets of 8-12 repetitions	The study's conclusion suggests that the increased cross-education observed after muscle lengthening training was likely due to a combination of sensory input and motor output mechanisms.
Hortobágyi et al. 1999 (Hortobgyi et al., 1999)	US	RCT	31	6 weeks	-	Voluntary or stimulated eccentric contractions	840 overall contractions	The increased strength gains observed both on the opposite and same sides of the body after electrical muscle stimulation EMS training are likely attributed to a combined impact of (EMS) and muscle lengthening, working together in an additive manner.
Kadri et al. 2017 (Kadri and No, 2017)	Algeria	RCT	36	8 weeks	3 sessions a week	43 isometric contractions of a 7-s duration for quadriceps femoris	43 isometric contractions	The proposed training program utilizing neuromuscular electrical stimulation (NMES) and voluntary (VOL) contractions led to strength gains in healthy young subjects. Still, they did not result in any improvement in contralateral mono pedal postural control. These findings indicate that while the training program can be therapeutically beneficial for increasing strength, it may not significantly impact postural control.

Kannus et al. 1992 (Kannus et al., 1992)	US	RCT	20	7 weeks	3 sessions a week	One-legged exercise on the strength, power, and endurance	-	The study demonstrated a nearly linear trend for endurance parameters, whereas the outcomes leaned towards a curvilinear pattern for strength and power parameters, showcasing limited advantages.
Kim et al. 2011 (Kim et al., 2011)	South Korea	RCT	32	2 weeks	4 sessions a week	Concentric isokinetic training exercises for the dominant side	5 sets of 10 repetitions	Contralateral training using unilateral isokinetic exercises could improve one-legged standing balance in the contralateral limb after a short duration of training.
Lagerquist et al. 2006 (Lagerquist et al., 2006)	Canada	RCT	16	5 weeks	3 sessions a week	Isometric extension maximal voluntary contractions	5 sets of 8 repetitions	They concluded that the cross-education effect observed in strength training was likely influenced more by supraspinal mechanisms rather than solely relying on spinal mechanisms.
Latella et al. 2012 (Latella et al., 2012)	Australia	RCT	18	8 weeks	3 sessions a week	Unilateral horizontal leg press strength training	3 sets of 8 repetitions	Corticospinal adaptations were fundamental in driving the improvements observed in cross-education gains in the lower limbs after unilateral strength training.
Lepley et al. 2014 (Lepley and Palmieri-Smith, 2014)	US	RCT	18	8 weeks	3 sessions a week	Eccentric contraction of the quadriceps	2 sets of 3 repetitions	Engaging in exercises involving eccentric actions led to specific improvements in quadriceps strength in the non-exercised limb, with effects specific to the exercise mode and velocity.
Manca et al. 2015 (Manca et al., 2015)	Italy	RCT	30	4 weeks	4 sessions a week	Unilateral isokinetic/concentric training of the stronger ankle dorsiflexion	3 sets of 4 repetitions	The cross-training effect was observed in the AD muscles, as evidenced by peak torque (PT) and muscle work (MW) improvements. Adding MW analysis provided valuable insights into muscle performance alongside PT analysis.
Mandal et al. 2023 (Mandal et al., 2023)	UK	RCT	35	8 weeks	3 sessions a week	Unilateral straight-leg calf raises targeting the gastrocnemii	3 sets of 12 repetitions	The study demonstrated that a straightforward unilateral plantar flexor exercise protocol, which could be performed at home, led to significant

								improvements in contralateral strength, muscular excitation, and power.
Maroto-Izquierdo et al. 2022 (Maroto-Izquierdo et al., 2022)	Spain	RCT	40	6 weeks	Twice a week	Dominant leg isoinertial squat training	4 sets of 7 repetitions	The three eccentric overload resistance training modalities resulted in similar neuromuscular changes in both the trained and non-trained legs, indicating the presence of cross-education solid effects induced by the eccentric-overload training.
Martínez et al. 2021 (Martnez et al., 2021)	Spain	RCT	36	6 weeks	3 sessions a week	Eccentric contraction of the dominant limb	3 sets of 8 repetitions	Cross-education training held significant potential for clinical applications and musculoskeletal and neuromuscular rehabilitation following unilateral injury.
Mendonca et al. 2021 (Mendonca and Vila, 2021)	Portugal	RCT	30	4 weeks	5 sessions a week	Dynamic plantar-flexion training	4 sets of 10 repetitions	Both training regimens could be used interchangeably to enhance contralateral rapid torque production. This flexibility in training methods could prove advantageous when limb immobilization was necessary following injury or surgery, facilitating a more balanced and comprehensive recovery process.
Razian et al. 2022 (Razian et al., 2022)	Iran	RCT	39	12 weeks	NR	Unilateral Non-Dominant Lower Limb Training and Unilateral Dominant Lower Limb Training	-	The findings of this study presented a new exercise and rehabilitation approach that could be utilized when one limb is affected or impaired.
Shima et al. 2002 (Shima et al., 2002b)	Japan	RCT	15	6 weeks	4 sessions a week	Unilateral flexion of plantar flexor muscles	3 sets of 10–12 repetitions	The mechanisms that account for the cross-education of muscular strength were. However, likely to be attributed to central neural factors during the training phase, although this explanation might not be the sole factor influencing the phenomenon during the detraining phase.

Tøien et al. 2017 (Tøien et al., 2018)	Norway	RCT	23	3 weeks	3 sessions a week	Dominant plantar flexors	4 sets of 4 repetitions	The cross-limb effects observed in older adults were influenced by the improvement in efferent neural drive, highlighting the clinical significance of contralateral training to enhance neuromuscular function in individuals with conditions leading to unilateral strength reductions.
Weir et al. 1995 (Weir et al., 1995)	US	RCT	17	8 weeks	3 sessions a week	Unilateral eccentric leg extension weight training	3-5 sets of 6 repetitions	The one-sided training led to heightened bilateral strength. The analyses, encompassing both individual-repetition maximum (I-RM) and isometric assessments, demonstrated that the effects of training endured even throughout an 8-week detraining period.
Weir et al. 1997 (Weir et al., 1997)	US	RCT	16	8 weeks	3 sessions a week	Unilateral concentric leg extension weight training	3-5 sets of 6 repetitions	The impact of detraining was notably more evident in isometric strength compared to individual-repetition maximum (I-RM) strength. This distinction was observed as a significant decline in isometric scores after training. In contrast, the detraining I-RM values did not substantially decrease from their post-training levels for either individual limb or bilateral assessments.

Table 2.2: Baseline of the included studies. BMI: body mass index.

Study ID	Study Groups	Sample	Age, years, M ± SD	Sex, Male, n (%)	Weight, Kg, M ± SD	Height, CM, M ± SD	BMI, Kg/m2, M ± SD
Abazovic et al. 2015 (Abazovc et al., 2015)	Unilateral non-dominant concentric training	15	19-25 (range)	All females	60.9 ± 7.1	168 ± 6.2	-
	Control	15					-
Carolan et al. 1992 (Carolan and Cafarelli, 1992)	Unilateral isometric extension training	10	21.4 ± 0.7	All males	76.2 ± 3.2	176.4 ± 4.7	-
	Control	10	22.1 ± 0.9		77.7 ± 3.6	177.9 ± 4.4	-
Colomer-Poveda et al. 2021 (Colomer-	Low-load resistance training to concentric muscular failure	11	20.8 ± 1.3	All males	-	-	-
	High-load resistance training to concentric muscular failure	11	21.4 ± 1.4		-	-	-

Poveda et al., 2021)	High-load resistance training without failure	11	21.8 ± 1.5		-	-	-
	Control	9	23.5 ± 4.3		-	-	-
Coratella et al. 2015 (Coratella et al., 2015)	Isokinetic	16	20.5 ± 2.3	All males	78.9 ± 5.3	180 ± 11	-
	Dynamic constant external resistance	16					-
	Control	17					-
Coratella et al. 2022 (Coratella et al., 2022)	Concentric training	15	22 ± 4	All females	60.2 ± 4.3	164 ± 6	-
	Eccentric training	15					-
	Traditional concentric–eccentric training	15					-
	Control	15					-
Evetovich et al. 2001 (Evetovich et al., 2001)	Unilateral concentric isokinetic leg extension training	11	22.2 ± 2.8	All males	-	-	-
	Control	9			-	-	-
	Traditional training	14	23 ± 3	12 (85.7)	73 ± 9	172 ± 7	25 ± 2
	Rest-redistribution	10	22 ± 2	8 (80)	74 ± 11	174 ± 8	24 ±2

Fariñas et al. 2023 (Farias et al., 2023)	Control	11	22 ± 2	9 (82)	73 ± 10	173 ± 7	25 ± 3
Fimland et al. 2009 (Fimland et al., 2009)	Unilateral strength training	15	24 ± 2	4 (27)	70 ± 11	175 ± 6	-
	Control	11	24 ± 1	5 (45.5)	70 ± 9	-	-
Garfinkel et al. 1992 (Garfinkel and Cafarelli, 1992)	Isometric resistance training	8	21.9 ± 2.7	All females	57.8 ± 12.4	164.1 ± 11.6	-
	Control	7					-
Goodwill et al. 2012 (Goodwill et al., 2012)	Strength training	7	21 ± 1.1	4 (57)	-	-	-
	Control	7	21 ± 1.2	3 (43)	-	-	-
Hosseinzadeh et al. 2015	Contralateral resistance training	13	26.9 ± 4.3	All males	77.5 ± 11.8	175.5 ± 5.8	25.1 ± 3.4
	Ipsilateral resistance training	13	27.2 ± 5.4		75.1 ± 7.6	177.4 ± 5.8	23.9 ± 2.3

(Hosseinzadeh et al., 2015)							
Hortobágyi et al. 1997 (Hortobgyi et al., 1997)	Eccentric training	7	21.3 ± 1.9	All males	75.4 ± 6.8	175.2 ± 2.6	-
	Concentric training	8					-
	Control	6					-
Hortobágyi et al. 1999 (Hortobgyi et al., 1999)	voluntary contractions	8	24.8 ± 4.5	All females	62.8 ± 8	163 ± 5	-
	Rectromyostimulation (EMS)	8					-
	Remote EMS	8					-
	Control	8					-
Kadri et al. 2017 (Kadri and No, 2017)	Electro-induced contractions	12	22.67 ± 2.74	All males	72.50 ± 10.31	177.50 ± 7.52	22.92 ± 1.89
	Voluntary contractions exclusively	12	21.83 ± 0.93		69.50 ± 6.54	178.25 ± 5.51	21.93 ± 2.52
	Control	12	22.50 ± 0.9		74.75 ± 9.54	178.17 ± 5.63	21.93 ± 2.52
	Strength training	10	29.5 ± 5	10 (50)	68 ± 12.3	172.3 ± 7	23 ± 2.8

Kannus et al. 1992 (Kannus et al., 1992)	Control	10	29.4 ± 6		67.4 ± 13	169.2 ± 7.6	23.4 ± 3.5
Kim et al. 2011 (Kim et al., 2011)	Unilateral hip isokinetic exercises	16	21 ± 0.4	6 (37.5)	56 ± 1.9	165 ± 1.3	-
	Control	16	22 ± 0.4	6 (37.5)	56 ± 2.4	162 ± 2	-
Lagerquist et al. 2006 (Lagerquist et al., 2006)	Isometric resistance training	10	21-42 (range)	4 (40)	-	-	-
	Control	6		3 (50)	-	-	-
Latella et al. 2012 (Latella et al., 2012)	Strength training	9	-	14 (77.8)	-	-	-
	Control	9	-		-	-	-
Lepley et al. 2014 (Lepley and Palmieri-Smith, 2014)	Eccentric training	9	23.3 ± 2.4	5 (55.6)	70.6 ± 14.3	173 ± 10	-
	Control	9	22.6 ± 3.6	3 (33.3)	66.9 ± 10	172 ± 10	-
	Isokinetic training	15	25.7 ± 5.4	10 (66.7)	67.1 ± 13.0	-	-

Manca et al. 2015 (Manca et al., 2015)	Control	15	27.7 ± 3.7	11 (63.6)	73.9 ± 10.2	-	-
Mandal et al. 2023 (Mandal et al., 2023)	Unilateral calf raises	20	20.7 ±1.3	9 (45)	62.8 ±16.3	166.2 ±7.3	-
	Control	14	21.4 ±1.8	7 (50)	61.5 ±14.0	164.4 ±8.3	-
Maroto-Izquierdo et al. 2022 (Maroto-Izquierdo et al., 2022)	Eccentric velocity of 100%	10	21.3 ± 1.1	All males	76.8 ± 8.2	180.0 ± 4.6	-
	Eccentric velocity of 150%	10	21.1 ± 0.6		74.8 ± 6.6	179.1 ± 6.0	-
	Concentric	10	21.4 ± 2.2		75.1 ± 8.9	175.8 ± 5.9	-
	Control	10	22.7 ± 3.4		76.7 ± 11.1	175.3 ± 5.1	-
Martínez et al. 2021 (Martnez et al., 2021)	Eccentric contraction runtime = 6 seconds	11	21.18 ± 2.19	-	67.14 ± 3.00	171 ± 2	-
	Eccentric contraction runtime = 3 seconds	12	21.33 ± 2.54	-	67.68 ± 2.79	169 ± 2	-

	Control	13	21.27 ± 2.76	-	67.22 ± 3.16	172 ± 2	-
Mendonca et al. 2021 (Mendonca and Vila, 2021)	High-intensity resistance training	15	21.9 ± 3.3	-	61.9 ± 9.3	166.4 ± 8.4	-
	Low-intensity resistance training	15	22.3 ± 2.9	-	64.7 ± 9.5	170.3 ± 8.4	-
Razian et al. 2022 (Razian et al., 2022)	Unilateral Dominant Lower Limb Training	13	60.0 ± 5.6	All females	70.6 ± 10	160.7 ± 0.07	27.4 ± 4.1
	Unilateral Non-Dominant Lower Limb Training	13	59.3 ± 5.8		68.6 ± 10.9	157.7 ± 0.1	27.6 ± 5.1
	Dominant Control	13	58.8 ± 0.3		68.2 ± 5.5	154.5 ± 0.1	28.59 ± 2.12
	Non dominant Control		58.8 ± 0.3		68.2 ± 5.5	154.5 ± 0.1	68.2 ± 5.5
Shima et al. 2002 (Shima et al., 2002b)	Resistance training	9	26.2 ± 4.6	All males	67 ± 6.5	172.6 ± 5.9	-
	Control	6	26 ± 3.6		66.8 ± 3.8	172.4 ± 5.2	-
	Maximal Strength Training	11	73 ± 4	All males	-	-	-

Tøien et al. 2017 (Tøien et al., 2018)	Control	12			-	-	-
Weir et al. 1995 (Weir et al., 1995)	Eccentric training	9	23.7 ± 2.6	All males	85 ± 8.1	-	-
	Control	8	23.9 ± 3.4		76.5 ± 12.1	-	-
Weir et al. 1997 (Weir et al., 1997)	Concentric training	8	24.1 ± 5	All males	78.4 ± 10.2	-	-
	Control	8	23.9 ± 3.4		76.5 ± 12.1	-	-

2.4.2 Risk of bias assessment

According to the ROB-2 tool, 61.29% of studies showed a low risk of bias in the randomisation process, while 22.58% showed some concerns, and 16.13% showed a high risk of bias. In terms of deviation from the intended interventions, 19.35% showed a low risk, and 80.65% showed some concerns. Regarding missing outcome data, the majority (96.77%) of studies demonstrated a low risk of bias, with only 3.23% showing a high risk of bias. All studies (100%) showed a low risk of bias in terms of measurement of the outcomes and the selection of reported outcomes. Overall, 22.58% of the studies showed a low risk of bias, 58.06% had some concerns, and 19.35% demonstrated a high risk of bias (Figure 2.2).

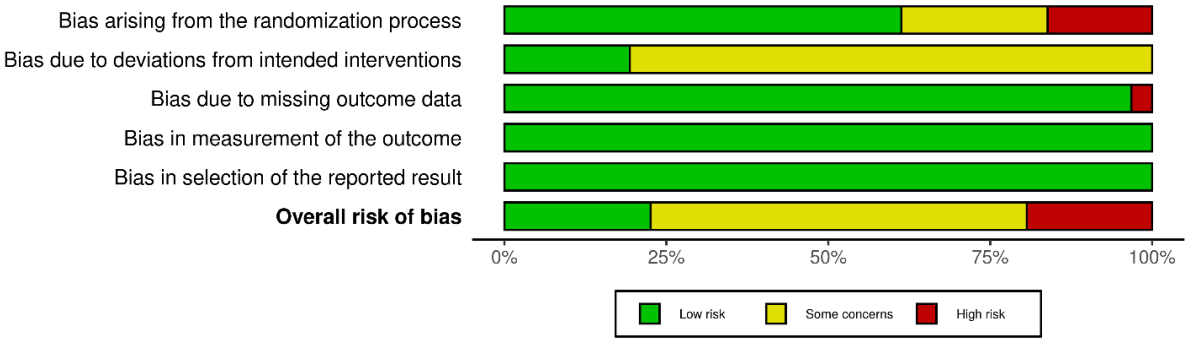


***Figure 2.2**: Risk of bias summary according to the Cochrane risk-of-bias tool for randomised trials (RoB 2).*

2.4.3 Summary of Findings and GRADE Assessment

The certainty of evidence was evaluated using the GRADE framework, and results are presented in the Summary of Findings and GRADE Assessment table (Table 2.1)

Table 2.3: *Summary of Findings and GRADE Assessment of Evidence Quality for Cross-Education Effects Following Unilateral Lower-Limb Resistance Training*

	Certainty assessment							№ of patients		Effect	Certainty	Importance
Outcome	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cross-education	Control	Absolute (95% CI)		
Change in One-repetition maximum (1RM)	6	randomised trials	serious[a]	very serious[b]	not serious	not serious	none	113	107	SMD **1.18 SD higher** (0.46 higher to 1.89 higher)	⨁◯◯◯ Very low	CRITICAL
Change in Maximum Voluntary Contraction	9	randomised trials	serious[a]	serious[b]	not serious	not serious	none	137	116	SMD **0.66 SD higher** (0.31 higher to 1.02 higher)	⨁⨁◯◯ Low	IMPORTANT
Change in Concentric peak torque	6	randomised trials	not serious	not serious	not serious	not serious	none	151	165	SMD **0.62 SD higher** (0.36 higher to 0.89 higher)	⨁⨁⨁⨁ High	IMPORTANT
Change in Eccentric peak torque	4	randomised trials	not serious	not serious	not serious	not serious	none	122	126	SMD **0.39 SD higher** (0.13 higher to 0.64 higher)	⨁⨁⨁⨁ High	IMPORTANT

	Certainty assessment							№ of patients		Effect	Certainty	Importance
Outcome	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cross-education	Control	Absolute (95% CI)		
Change in isometric peak torque	7	randomised trials	serious[a]	not serious	not serious	not serious	none	223	224	SMD **0.45 SD higher** (0.26 higher to 0.64 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Change in pennation angle	2	randomised trials	not serious	not serious	not serious	serious[c]	none	30	28	SMD **0.25 SD higher** (0.27 lower to 0.77 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Change in Muscle Thickness	3	randomised trials	not serious	not serious	not serious	serious[c]	none	39	37	SMD **0.01 SD higher** (0.44 lower to 0.46 higher)	⨁⨁⨁◯ Moderate	NOT IMPORTANT

CI: confidence interval; **SMD:** standardised mean difference

Explanations

a. One study has a high risk of selection bias

b. Moderate Heterogeneity

c. Confidence intervals include appreciable benefit or harm

2.4.4 One-repetition maximum (1-RM)

Six studies were included with 10 data sets in the analysis of change in 1-RM. The random-effects model shows that cross-education through RET interventions was associated with significantly increased 1-RM compared to the control group (SMD: 0.59, 95% CI: 0.22 to 0.97; p=0.002), albeit with very low certainty (Figure 2.3a). The pooled data were low heterogeneous [Tau²=0.16; Chi²=16.01, p=0.07; I² = 44%]. After performing sensitivity analysis and excluding Martnez et al., 2021(Martnez et al., 2021) the heterogeneity was resolved [Tau²=0.00; Chi²=1.60, p=0.98; I²=0%] and the effect size remained significant (SMD: 0.33, 95% CI: 0.02 to 0.63; p=0.04) (Figure 2.3b).

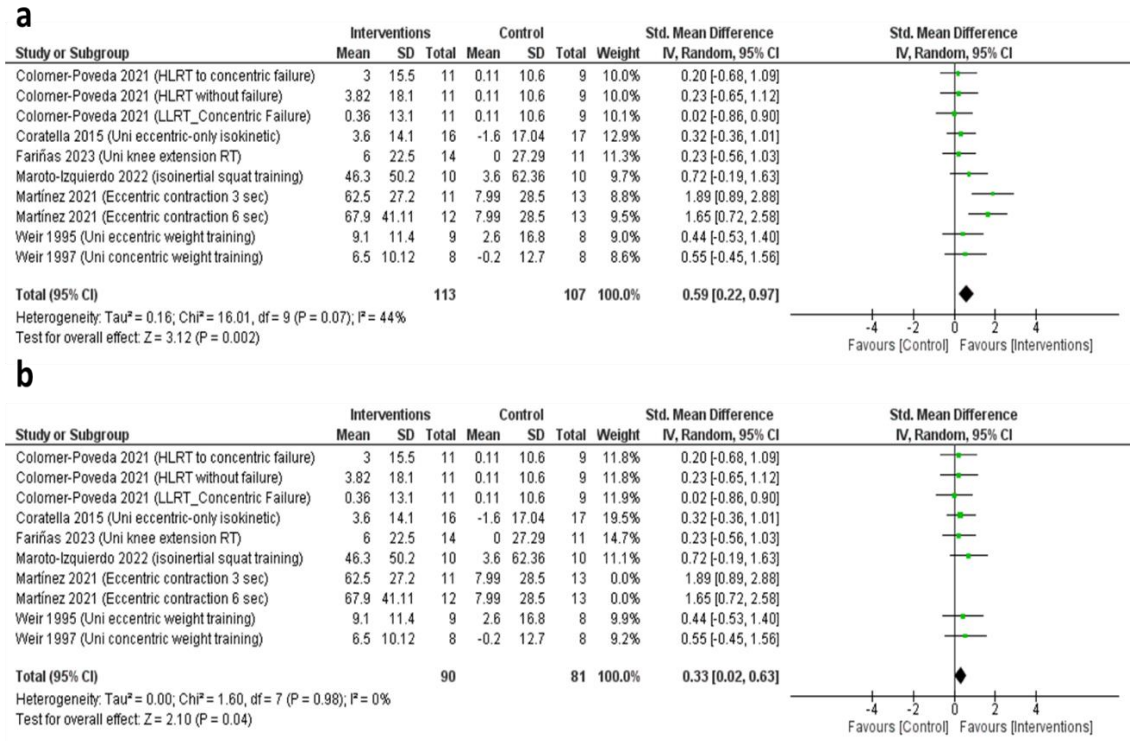


Figure 2.3: Forest plots of a) Random-model standardised mean difference for one-repetition maximum (1-RM), and b) 1-RM after the application of sensitivity analysis.

2.4.5 Maximum Voluntary isometric Contraction (MVC)

Nine studies were included with 12 data sets in the analysis of the change in MVC. The pooled random-effects model shows that cross-education through RET interventions was associated with significantly increased MVC compared to the control group (SMD: 0.55, 95% CI: 0.16 to 0.94; p=0.006), albeit with low certainty (Figure 2.4a). The pooled data were moderately heterogeneous [Tau^2=0.26; Chi^2=24.41, p= 0.01; I^2=55%]. After performing the sensitivity analysis and excluding Carolan et al., 1992 (Carolan and Cafarelli, 1992) the heterogeneity was low [Tau^2=0.17; Chi^2=18.26, p=0.05; I^2=45%], and the effect size remained significant (SMD: 0.45, 95% CI: 0.08 to 0.82; p=0.02) (Figure 2.4b).

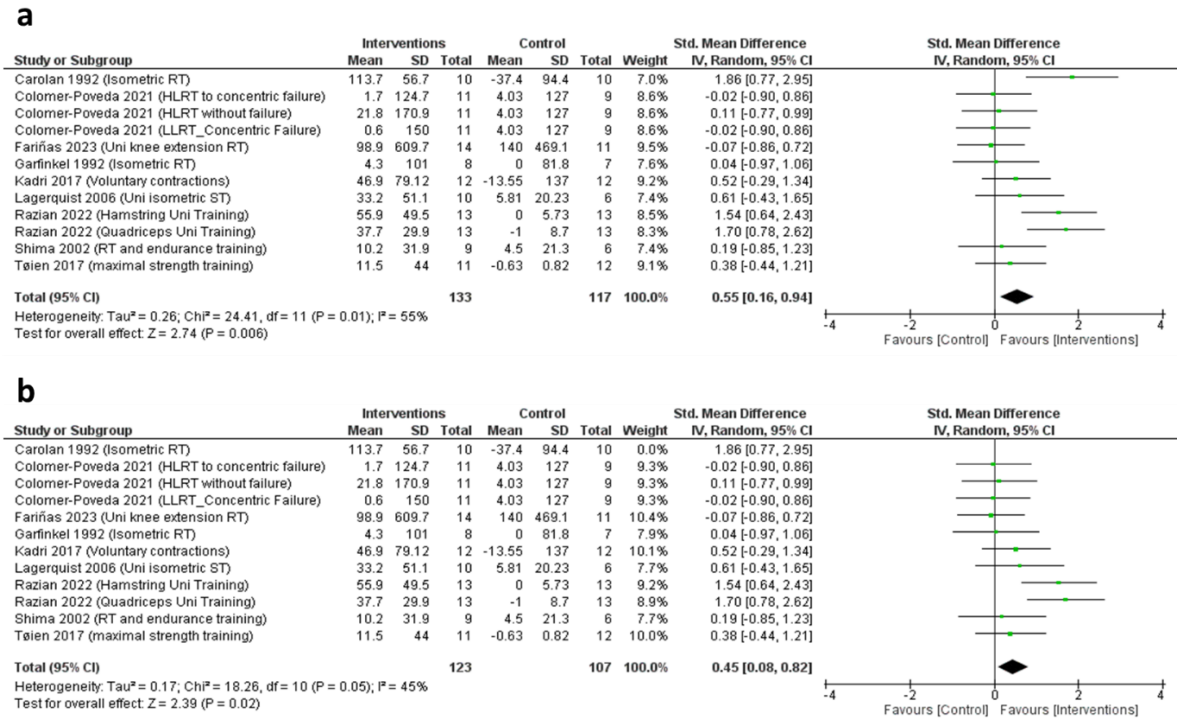


Figure 2.4a) Forest plot of random-model standardised mean difference of maximum voluntary contraction (MVC), b) Forest plot of MVC after the application of sensitivity analysis.

2.4.6 Concentric Peak Torque

Six studies were included with 13 data sets in the analysis of change for concentric peak torque, which is the maximum force a muscle can generate during shortening. The pooled random-effects model shows that cross-education through RET interventions was associated with significantly increased concentric peak torque compared to the control group (SMD: 0.62, 95% CI: 0.38 to 0.86; $p<0.00001$) with high certainty (Figure 2.5a). The pooled data were homogenous [$Chi^2=13.81$, $p=0.31$; $I^2=13\%$].

2.4.7 Eccentric Peak Torque

Four studies were included with 10 statistical sets in the analysis of change for eccentric peak torque, which is the maximum force a muscle can generate during lengthening. The pooled random-effects model shows that cross-education through RET interventions was associated with significantly increased eccentric peak torque compared to the control group (SMD: 0.39, 95% CI: 0.13 to 0.65; $p=0.003$) with high certainty (Figure 2.5b). The pooled data were homogenous [$Chi^2 = 9.33$, ($P = 0.41$); $I^2 = 4\%$].

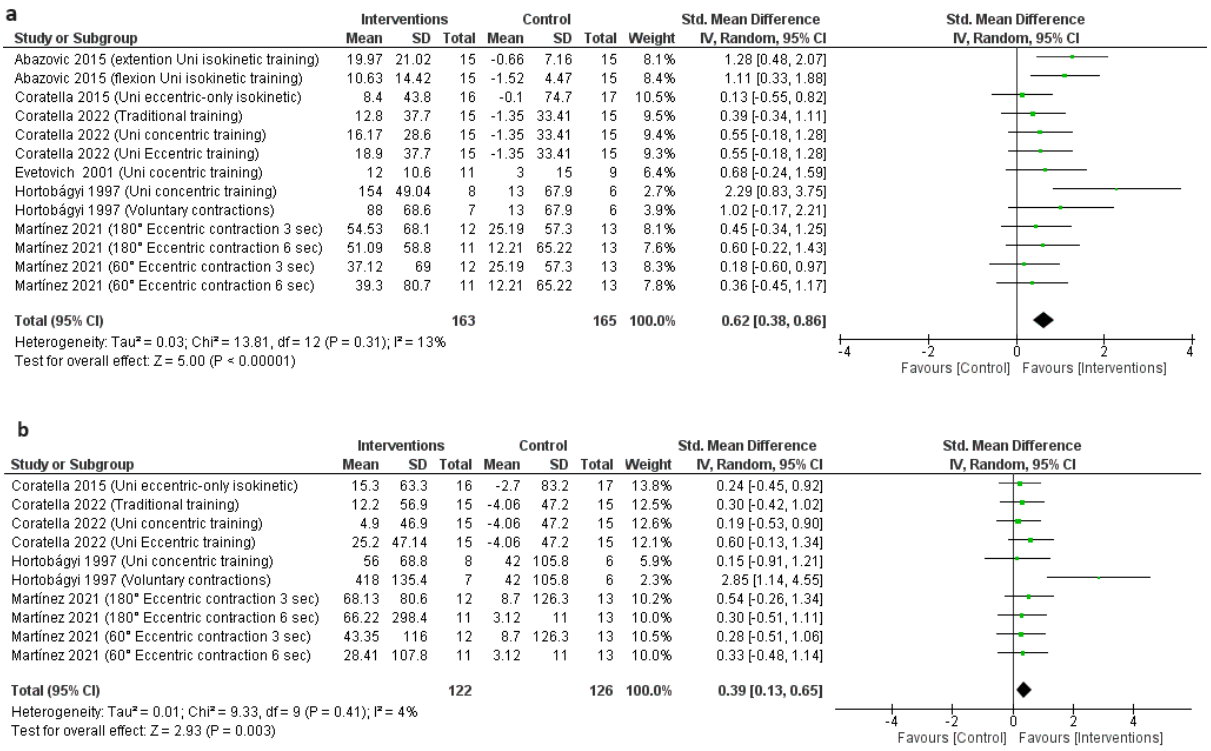


Figure 2.5: Forest plots of random-model standardised mean difference (SMD) of a) concentric and b) eccentric peak torque.

2.4.8 Isometric Peak Torque

Seven studies were included with 20 statistical sets in the analysis of change for isometric peak torque, which is the maximum force a muscle can generate while it remains at a constant length. The pooled random-effects model shows that cross-education through RET interventions was associated with significantly increased isometric peak torque compared to the control group (SMD: 0.45, 95% CI: 0.26 to 0.64; p<0.00001) with moderate certainty (Figure 2.6). The pooled data were homogenous [$Chi^2 = 10.43$, ($P = 0.94$); $I^2 = 0\%$].

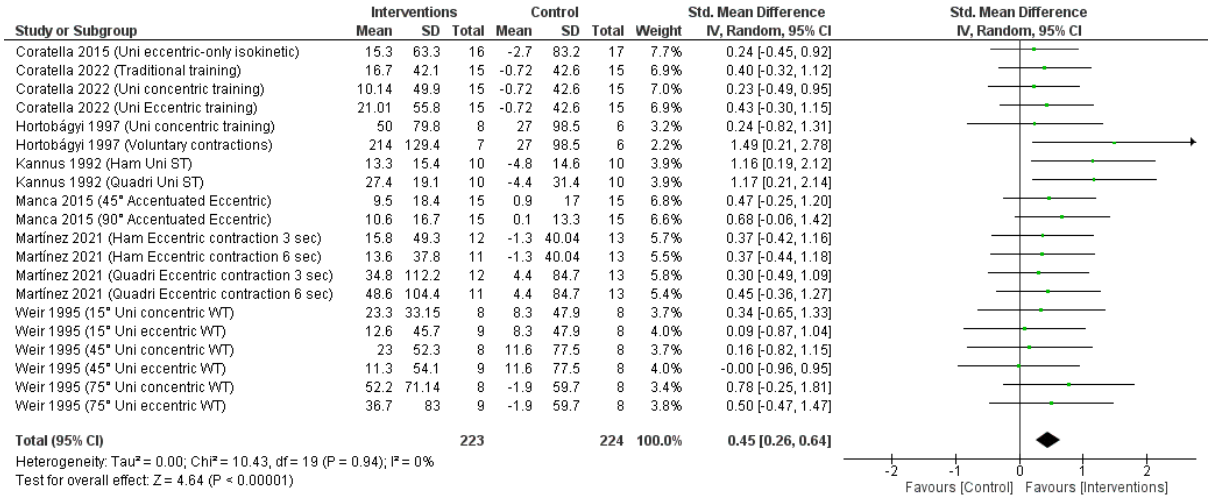


Figure 2.6Forest plot of random-model standardised mean difference (SMD) of isometric peak torque.

Subgroup analysis according to the type of training (eccentric, concentric or 'other') was only possible for isometric peak torque. This analysis showed that eccentric and 'other' training were associated with significantly increased isometric peak torque compared to the control group (SMD: 0.37, 95% CI: 0.13 to 0.61; p=0.003 and SMD: 0.91, 95% CI: 0.42 to 1.39; p=0.0002, respectively). Concentric training was not significantly different to the control group (SMD: 0.33, 95% CI: -0.09 to 0.74; p=0.12) (Figure 2.7).

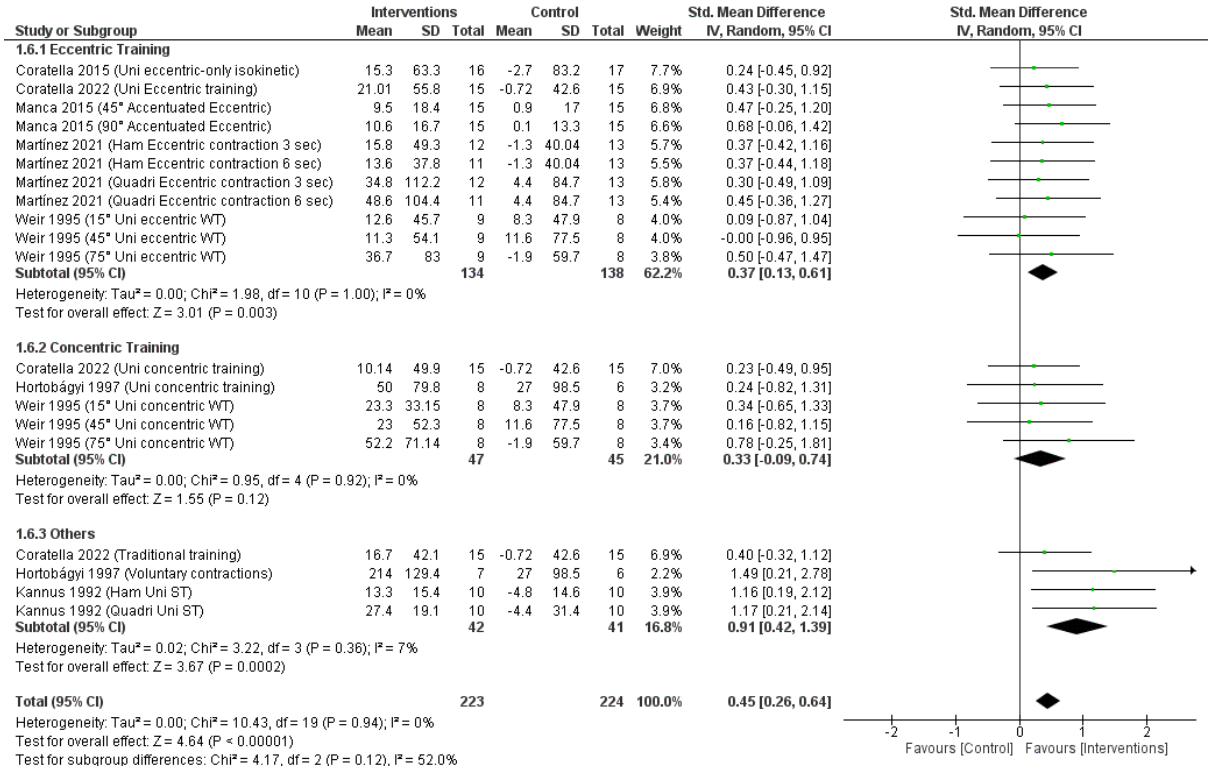


Figure 2.7Forest plot of random-model standardised mean difference (SMD) of isometric peak torque for eccentric, concentric or 'other' training.

2.4.9 Pennation Angle

Two studies were included for analysis of change in pennation angle. The pooled random-effects model shows that there was no cross-education through RET interventions, with no difference in pennation angle between the two groups (SMD: 0.25, 95% CI: -0.27 to 0.77; p=0.35, moderate certainty) (Figure 2.8a). The pooled data were homogenous [$Chi^2 = 0.26$, ($P = 0.61$); $I^2 = 0\%$].

2.4.10 Muscle Thickness

Three studies were included for analysis of change in muscle thickness. The pooled random-effects model shows that there was no difference in muscle thickness between the

two groups (SMD= 0.01, 95% CI: -0.44 to 0.46; p=0.97, moderate certainty) (Figure 2.8b). The pooled data were homogenous [Chi² = 0.27, (P = 0.88); I² = 0%].

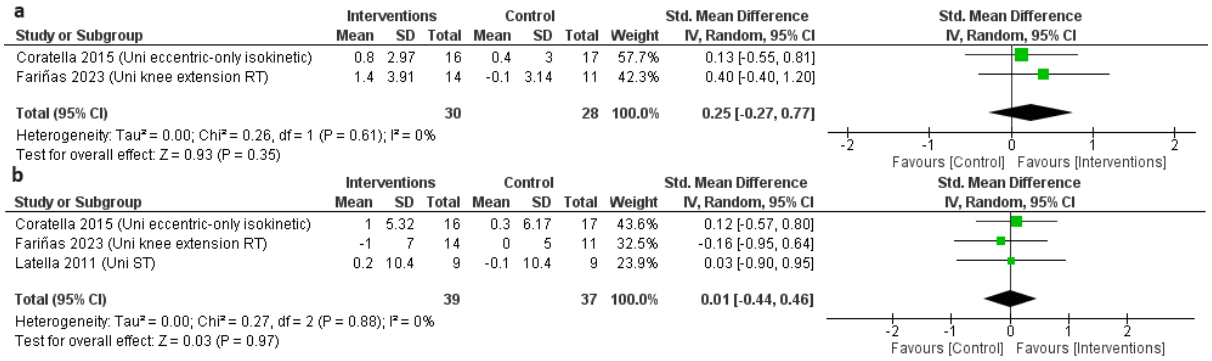


Figure 2.8Forest plot of random-model standardised mean difference (SMD) for a) pennation angle and b) muscle thickness.

2.4.11 Subgroup Analysis According to Sex

In sex-based subgroup analysis, male participants showed a significant increase in 1-RM with contralateral training (SMD: 0.34, 95% CI: 0.01 to 0.67; p=0.04), with insufficient data to explore females. Regarding MVC, a significant increase was observed for females only (SMD: 1.12, 95% CI: 0.13 to 2.11; p=0.03). For concentric peak torque, both females (SMD: 0.75, 95% CI: 0.41 to 1.09; p<0.0001) and males (SMD: 0.86, 95% CI: 0.06 to 1.65; p=0.03) demonstrated a significant increase. Regarding isometric peak torque, a significant increase was also only demonstrated for females (SMD: 0.43, 95% CI: 0.06 to 0.80; p=0.02). It was not possible to explore eccentric peak torque for either sex due to insufficient data. Full details of this subgroup analysis are shown in Table 2.4.

Table 2.4: Subgroup analysis according to sex. Abbreviations: CI, confidence intervals; 1-RM, one-repetition maximum; MVC, maximum voluntary contraction; CPT, concentric peak torque; IPT, isometric peak torque.

Outcome	Subgroup	Model	SMD [95% CI]	P-value	Heterogeneity
1-RM	Males	Random	0.34 [0.01, 0.67]	0.04	Tau^2=0.00; Chi^2=1.54, (p=0.96); I^2=0%
	Both		1.23 [0.16, 2.29]	0.02	Tau^2=0.67; Chi^2=8.32, (p=0.02); I^2 = 76%
MVC	Males	Random	0.39 [-0.04, 0.81]	0.08	Tau^2=0.12; Chi^2=9.30, (p=0.16); I^2 = 35%
	Females		1.12 [0.13, 2.11]	0.03	Tau^2=0.54; Chi^2=6.67, (p=0.04); I^2=70%
	Both		0.18 [-0.46, 0.82]	0.58	Tau^2= 0.01; Chi^2=1.03, (p=0.31); I^2=3%
CPT	Males	Random	0.86 [0.06, 1.65]	0.03	Tau^2=0.38; Chi^2=7.43, (p=0.06); I^2=60%

	Females		0.75 [0.41, 1.09]	<0.0001	Tau^2 = 0.00; Chi^2 = 4.05, (p=0.40); I^2=1%
IPT	Males	Random	0.28 [-0.06, 0.63]	0.11	*** Chi^2=1.69, (p=0.95); I^2=0%
	Females		0.43 [0.06, 0.80]	0.02	*** Chi^2=3.05, (p=0.55); I^2=0%
	Both		0.57 [0.29, 0.86]	<0.0001	*** Chi^2=4.08, (p=0.77); I^2 = 0%

2.5 Discussion

This systematic review and meta-analysis reports on cross-education for multiple aspects of muscle function and structure. The findings highlight that cross-education can improve both static and dynamic muscle strength and does not alter muscle structure (pennation angle or muscle thickness). These findings align with prior analyses that also report the potential of cross-education for promoting strength, including a previous meta-analysis of 31 studies showing that unilateral RET was associated with a significant increase in the strength of contralateral upper (MD: 9.35, 95% CI: 6.26 to 12.43) and lower limbs (MD: 16.4, 95% CI: 12.30 to 20.49) (Manca et al., 2017b). Although this analysis was conducted on 31 studies; only 17 of these studies focused on the lower limb. As such, for our specific

question, which is focused on the lower limb only, this review is markedly more comprehensive, including 29 studies on the lower limb only. In addition, we have assessed several outcomes related to muscle function, including muscle structure, with sub-analysis based on sex. In comparison, this previous review by Manca et al., assessed the impact of cross-education on muscle strength only (Manca et al., 2017b). Similarly, another meta-analysis by Carroll et al., also only reported the effect of cross-education on lower limb strength, again concluding that strength increases can occur, albeit at approximately half the magnitude of that seen in the trained limb (Carroll et al., 2006b). Finally, Munn et al., showed that cross-education was associated with a significantly increased muscle strength in the untrained limb, however, this study was published in 2004 and only included 17 studies across both upper and lower limbs (Munn et al., 2004).

The exact biological processes facilitating the transfer of muscle strength to the contralateral limb after RET remain unidentified, despite several attempts to explain this phenomenon. Carroll et al., (Carroll et al., 2006b) proposed two potential mechanisms: i) Cross-Activation Hypothesis: “spillover” of neural drive to the untrained side, prompting changes in its control system, and ii) Bilateral-Access Hypothesis: neuromuscular adaptations in the control system for the trained limb that can be accessed by the opposite limb. It is possible that the central nervous system enhances its motor neuron activation patterns in response to unilateral RET, which subsequently benefits the untrained limb by optimising motor unit recruitment and synchronisation. There is, of course, also the possibility that these two purported mechanisms may coexist and together contribute to the observed effects. This potential for multiple mechanisms and the typically subtle nature of the contralateral strength training effect may account for the current challenges in pinpointing the exact physiological roots of this effect. Further suggestions relating to

mechanisms include the notion that cross-education might be mediated by alterations in the excitability of ipsilateral projections; nerve pathways that originate and terminate on the same side of the body. In support of this, early studies, such as those by Hoff & Hoff in 1934, showed that damage to one area of the brain led to bilateral degeneration in certain brain regions, indicating the presence of ipsilateral projections (Hoff and Hoff, 1934). More recent anatomical tracer studies in macaques have confirmed extensive ipsilateral innervation from pyramidal tract projections (Yoshino-Saito et al., 2010, Soteropoulos et al., 2011). These ipsilateral projections include fibres that don't cross at the pyramidal decussation and those that cross and later recross the midline in the spinal cord. It is proposed that during unilateral actions, these ipsilateral projections might alter the excitability of spinal motoneurons of the opposite limb. Specifically, non-decussated pyramidal tract projections, which are a small proportion of corticofugal fibres that don't cross at the pyramidal decussation, might play a role in cross-education, especially for the lower limbs (Yoshino-Saito et al., 2010, Baker et al., 2015). Although not the focus of this review, while non-decussated projections in the dorsolateral funiculus might be involved in cross-education for the lower limbs, the role of ipsilateral projections in cross-education for the upper limbs remains uncertain (Baker et al., 2015).

Clearly, muscle adaptations during RET play a key role in enhancing the ability of the body to generate force (Bandy et al., 1990). Such adaptations include alterations in muscle enzyme concentrations (Deane et al., 2023), muscle hypertrophy due to enhanced muscle protein synthesis (Figueiredo, 2019), and alterations in the contractile protein composition of muscle, including, for example, shifts in fibre-type distribution (Bandy et al., 1990). Notably, cross-education has been observed to preserve muscle size and strength during periods of limb immobilisation (Haggert et al., 2020). However, to date, research studies

that have employed anthropometric (Muellbacher et al., 2000), imaging (Narici et al., 1989, Ploutz et al., 1994) or histological approaches (Hortobagyi et al., 1996) to measure muscle fibre type or muscle size have not found changes in the contralateral limb following unilateral RET. Therefore, while cross-education is primarily attributed to neural/neuromuscular factors, the potential for muscle-level adaptations should not be entirely discounted. It is plausible that current techniques applied in the available studies may not be sensitive enough to detect minor, yet functionally significant, changes.

One alternative consideration beyond neural factors is that changes in the contralateral limb during unilateral RET could be due to changes in the hormonal environment of the muscle. Anabolic hormonal shifts, which arise from RET, have been shown to impact untrained muscles (Kraemer and Ratamess, 2005). However, if hormones are a primary contributor to cross-education, it is challenging to reconcile why the effect specifically targets counterpart muscles (i.e., the same muscles on the opposite side of the body) in the contralateral limb, with several studies showing that non-counterpart muscles do not benefit from RET (Yue and Cole, 1992, Herbert et al., 1998). Further, it is challenging to understand how significant muscle changes could arise without some degree of motor unit contribution.

The suggestion that cross-education is primarily attributed to neural mechanisms only is also supported by the untrained limb showing no hypertrophy or structural adaptations after RET (Evetovich et al., 2001, Farthing et al., 2005). For example, Shima et al., reported increased neural drive to the untrained limb, evidenced by enhanced EMG activity (Shima et al., 2002a). Conversely, Lagerquist et al., reported increased neural responsiveness in the trained limb only, suggesting that cross-education mainly arises from supraspinal mechanisms (Lagerquist et al., 2006). Lee et al., further supported the suggestion of cortical

contribution to cross-education, but did not explore spinal cord-level adaptations (Lee and Carroll, 2007c).

Considering our subgroup analysis of RET comprised of different contraction types (i.e., concentric, eccentric and 'other'), our finding of eccentric training being more effective than concentric training for eliciting cross-education in terms of isometric peak torque is similar to that previously reported by Manca et al., in relation to strength (Manca et al., 2017b). Specific reasons for this are not clear; however, eccentric contractions elicit different neural effects than concentric contractions immediately following acute loading (Jones et al., 2023), possibly due to differences in the level of accumulated metabolites acting on efferent inhibitory pathways. The decreased excitability of descending corticospinal pathways and greater autogenic motoneuron inhibition during eccentric training may also influence cross-education (Aagaard, 2018).

Our sex-based subgroup analysis suggests that females may benefit more from RET-induced cross-education in terms of muscle strength; however, this is far from conclusive and requires further sex-specific comparisons. This could be attributed to oestrogen, a hormone found in higher abundance in females, which has been shown to influence both neural adaptation and muscle recovery (Dam et al., 2020). Specifically, the neuroprotective effects of oestrogen may enhance the brain's ability to adapt to unilateral training, enhancing the cross-education effect (Lee and Carroll, 2007c). However, further studies are needed to confirm this finding and investigate the contributing factors.

2.5.1 Clinical Implications

The findings from this review highlight the potential of 'exercise as medicine' in situations where bilateral function is not possible. This concept is already evidenced, with cross-education effects observed in stroke patients following dorsiflexion training with the less

affected limb (Dragert and Zehr, 2013). Moreover, there is increasing interest in the benefits of cross-education following anterior cruciate ligament reconstruction (ACLR), with evidence pointing towards its efficacy in preserving muscle function and aiding recovery (Andrushko et al., 2023). These findings align with this review's emphasis on the key functional roles of the lower limbs, particularly in older adults and vulnerable patient cohorts. Furthermore, the sex-specific differences suggested in this review, possibly favouring cross-education effects in females who are more susceptible to neuromuscular dysfunction with advancing age (Gale et al., 2018, Zhang et al., 2018, Piasecki et al., 2024, Guo et al., 2024) and who also face a disproportionate burden of stroke mortality and disability (Rexrode et al., 2022)- a condition most commonly associated with unilateral impairment (Cauraugh and Kim, 2003).

2.5.2 Experimental Advances

The inclusion of six further studies published within the past four years significantly enhances this meta-analysis beyond the last published. This larger sample size increases statistical power, allowing for more reliable and nuanced conclusions. However, mechanistic insight into cross-education is still lacking, and future studies aiming to expand the data pool and improve the ability to detect specific treatment effects should also explore probable mechanisms.

2.5.3 Limitations

Despite the relatively large sample size of included studies and the quality of these studies, there are some limitations to this review that should be acknowledged. The lack of mechanistic insight offered by the included studies is one such limitation. Although this does not impact our conclusions regarding the impact of RET on lower limb cross-education, it does hinder a full understanding of the underlying physiological processes. In

addition, we could not conduct subgroup analysis based on age due to insufficient data, which may dampen the clinical relevance of our findings (i.e., the implications for older adults as a specific cohort). Although heterogeneity in some outcomes is another limitation, sensitivity analysis and subgroup analysis were performed to address this issue.

A limitation of the review is that the inclusion criteria required studies to include a control group, even though the pooled meta-analysis did not use data from those control arms. This criterion improved methodological quality but may have excluded otherwise relevant unilateral training studies that lacked a control condition but still reported contralateral strength changes. Consequently, the findings of this review may slightly underestimate the total number of studies demonstrating cross-education effects.

Although subgroup analyses were conducted for training type and participant sex, other potentially relevant moderators, including age, training duration, and intensity, could not be analysed due to limited reporting across studies. This restricts the ability to fully determine how these variables influence the magnitude of cross-education.

2.5.4 Conclusion

In conclusion, this systematic review and meta-analysis emphasises the potency of cross-education for improving multiple static and dynamic aspects of muscle function. Future studies are required to better understand the likely intricate and multi-factorial mechanisms facilitating these enhancements, paving the way for optimised rehabilitation protocols in clinical situations where unilateral training has the potential to improve patient-centred and clinical outcomes.

Chapter 3: Effects of unilateral force accuracy training of the knee extensors on bilateral neuromuscular function in older adults

3.1 Abstract

Ageing is associated with impairments in motor-unit (MU) behaviour, force steadiness (FS), and motor control, contributing to functional decline and increased fall risk. Force Accuracy Training (FAT) is a novel, low-load intervention designed to enhance neural control without imposing high mechanical stress. This study aimed to investigate neuromuscular adaptations to a 4-week unilateral FAT intervention targeting the vastus lateralis (VL) in healthy older adults.

Sixteen older adults (73.8 ± 5.1 years; 8 female) performed low-intensity sinusoidal isometric knee extensions with their dominant leg, while the contralateral limb served as a within-subject control. Assessments were conducted pre-, post-, and at 2 and 4 weeks post-training. Outcomes included maximal voluntary contraction (MVC), FS, sinusoidal force-tracking accuracy (FTA), and functional measures (jump power, balance, Timed Up-and-Go). High-density surface electromyography (HDsEMG) was used to assess MU discharge rate (MUDR) and variability.

FAT elicited significant bilateral improvements in neuromuscular function. MVC increased by 10–15 % in the trained leg and 5–7 % in the untrained leg ($p < 0.01$), while FS improved by 20–30 % ($p < 0.001$) and sinusoidal FTA increased significantly ($p < 0.01$). HDsEMG revealed that MUDR was preserved in the trained VL but declined in the untrained limb, and MUDR variability decreased by ~15 % ($p < 0.01$) in the trained muscle, indicating enhanced temporal precision of MU firing and confirming a predominantly neural mechanism. Functional outcomes, including jump power, balance, and mobility, also improved following training.

Four weeks of unilateral FAT improved neuromuscular precision, force steadiness, and strength in older adults, with evidence of cross-education and partial retention after detraining. These findings demonstrate that low-load FAT enhances bilateral motor control and functional performance through neural adaptation, supporting its use as a feasible, neural-focused intervention to preserve independence and reduce fall risk in ageing populations.

3.2 Introduction

There is an escalating urgency to identify effective methods for preserving neuromuscular health, as the global population of older adults continues to grow. Preserving strength and motor control is vital not only for maintaining physical independence but also for minimising the likelihood of falls, disability, and reliance on long-term care (Hunter et al., 2016). The deterioration of skeletal muscle size and performance, referred to as sarcopenia, significantly contributes to frailty and functional decline in older adults (Cruz-Jentoft et al., 2019a).

Traditionally, sarcopenia research has focused on muscle atrophy; however, there is growing recognition that impairments in neuromuscular control, particularly within the motor unit (MU), play a major role in functional loss, independent of muscle size (Del Vecchio et al., 2019). Since motoneurons functionally govern muscle fibres, age-related changes in motor unit discharge rate (MUDR) and increased variability in discharge patterns have been shown to disrupt force steadiness (FS) and muscle coordination (Enoka and Farina, 2021). These changes are especially evident in the vastus lateralis, a key lower limb muscle, where substantial MU remodelling and discharge irregularity have been observed in older adults (Piasecki et al., 2016d, Piasecki et al., 2016c, Jones et al., 2022).

While previous studies have evaluated the functional effects of neuromuscular training, few have directly examined adaptations in MU discharge properties in response to low-intensity exercise. This study applies high-density surface electromyography (HDsEMG) to characterise adaptations in MU discharge behaviour within the vastus lateralis (VL), offering mechanistic insight into how low-load force accuracy training (FAT) influences motor control and FS in older adults.

3.2.1 The significance of the vastus lateralis

The VL is the largest and most functionally important part of the quadriceps femoris muscle group. It plays a vital role in locomotion, maintaining posture, and executing daily activities (ADLs) like walking, climbing stairs, and getting up from a chair (Piasecki et al., 2016d). Among lower limb muscles, the quadriceps, particularly the VL, are disproportionately affected by age-related atrophy, experiencing greater losses in muscle mass and function compared to more distal muscles such as the tibialis anterior (TA) (Maden-Wilkinson et al., 2015). Reductions in the cross-sectional area (CSA) and strength of the VL have been strongly associated with slower gait speed, impaired balance, and an elevated risk of falls (Studenski et al., 2011, Reid and Fielding, 2012). Because it is easily accessible for electromyography (EMG) and plays a crucial role in mobility, the VL is a valuable model for studying neuromuscular changes and testing strategies to help maintain independence in older adults.

A separate chapter explores FAT adaptations in the TA to contrast the effects in a more preserved distal muscle, thereby enabling muscle-specific comparisons across the ageing neuromuscular system.

3.2.2 Resistance exercise training

Resistance exercise training (RET) is widely regarded as the most effective strategy for mitigating sarcopenia and promoting neuromuscular adaptations (Phillips et al., 2017b, Mcleod et al., 2019). RET has been shown to increase muscle strength, enhance MU recruitment, and improve discharge rate (DR) modulation, all of which contribute to better force control and balance (Hunter et al., 2016, Elgueta-Cancino et al., 2022). However, older adults often exhibit anabolic resistance, a diminished muscle protein synthesis response to exercise, which limits hypertrophic gains despite training (Breen et al., 2013, Phillips et al., 2017b). Additionally, high-load RET can be challenging for older adults, comorbidities and joint pain may reduce tolerance, and adherence to recommended exercise schedules remains low (Baxter et al., 2024, Moseng et al., 2020a).

Pharmacological interventions aimed at preserving muscle mass and neuromuscular function, such as mTOR inhibitors (e.g., rapamycin) and myostatin inhibitors, have shown promise in preclinical studies. For example, (Lund et al., 2020) demonstrated that partial inhibition of mTORC1 in aged rats enhanced muscle mass and preserved neuromuscular junction (NMJ) structure, while (Ham et al., 2020) reported that chronic rapamycin treatment mitigated age-related NMJ degeneration in mice. Myostatin inhibitors have also driven substantial muscle growth in animal models, yet human clinical trials have produced inconsistent outcomes, showing minimal functional benefits and raising unresolved safety concerns (Wetzlich et al., 2025). In particular, long-term mTOR inhibition is associated with adverse effects, including immunosuppression, impaired glucose metabolism, and delayed wound healing, which constrains its clinical applicability in older adult populations (Zhu et al., 2016, Wilkinson et al., 2018). This points to the need for safer, more practical

options, such as low-load exercises targeting neuromuscular function, to help maintain muscle and MU health without the risks tied to drug-based therapies.

3.2.3 Force accuracy training: a neuromuscular precision approach

FAT is a novel approach that involves low-intensity, isometric sinusoidal contractions requiring precise modulation of force output. Rather than being designed solely to enhance fine motor control, FAT aims to challenge motor control across periods of MU recruitment and de-recruitment, thereby engaging both central and peripheral neural mechanisms responsible for force modulation (Christou, 2011, Christou and Enoka, 2011a, Knight and Kamen, 2007). By improving FS and reducing variability in motor output, FAT may contribute to enhanced functional movements that are critical for fall prevention and mobility in older adults.

Neural adaptations, such as reduced MU discharge variability, refined recruitment strategies, and enhanced central motor drive, underpin gains in force accuracy (Ely et al., 2022). In the VL, such changes are vital for supporting ADLs like balance, efficient walking, and rising from a chair.

3.2.4 Cross-education and neural plasticity

The phenomenon of cross-education (CE), the transfer of strength and neuromuscular adaptations from a trained limb to its contralateral untrained counterpart, has significant implications for older adults, particularly those with unilateral weakness or injury (Lee and Carroll, 2007b). CE effects are thought to arise from neural adaptations at both cortical and spinal levels, including increased excitability of motor areas, enhanced interhemispheric communication, and improved MU activation patterns in the untrained limb (Farthing, 2009).

For older adults, where injury or frailty may make direct training difficult, CE could serve as a safe and practical way to improve function in an affected limb. By using a split-body design, this study directly examines these effects in a healthy ageing population, highlighting the potential of FAT for clinical and rehabilitation settings.

3.2.5 Exercise retention

While the short-term benefits of exercise are well known, how well neuromuscular adaptations are retained after stopping training (detraining) is still not well understood in older adults. Evidence suggests that neural mechanisms, including cortical drive and MUs recruitment, may play a larger role in preserving strength than structural muscle mass alone (Clark et al., 2014). In fact, recent detraining studies indicate that neuromuscular improvements can persist longer than hypertrophic gains (Baxter et al., 2024). Understanding FAT-induced neural adaptation is, therefore, crucial for optimising exercise strategies in older adults.

3.2.6 Study aims

This chapter focuses on evaluating the effectiveness of a 4-week unilateral FAT intervention targeting the VL in healthy older adults aged 65–85 years. The primary objective is to assess changes in neuromuscular function, MU discharge properties, FS, and functional performance following the intervention. A secondary objective is to examine the presence and extent of cross-education effects and to explore the retention of neuromuscular adaptations after a 4-week detraining period.

It was hypothesised that FAT would significantly improve neuromuscular function in the trained VL, as reflected by increased MUDR, reduced discharge variability, improved FS, and enhanced strength. Secondary effects in the contralateral limb were anticipated,

consistent with CE mechanisms. Furthermore, these adaptations were expected to persist following a short period of detraining. This chapter investigates these outcomes using a split-body design, high-density surface electromyography (HDsEMG), and a comprehensive set of functional assessments to capture both local and systemic neuromuscular changes.

3.3 Methods

3.3.1 Ethical approval

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (WMA, 2013). Ethical approval was obtained from the Institutional Review Board (IRB) of the University of Nottingham Faculty of Medicine and Health Sciences Research Ethics Committee, under approval number FMHS 390-1121. The full ethics application for this study can be seen in Appendix II.

Before participating, each individual received a comprehensive explanation of the study's objectives, procedures, potential risks, and benefits. Participants were informed that their involvement was voluntary and that they had the right to withdraw from the study at any time without penalty. Written informed consent was obtained from all participants, ensuring their understanding and agreement to take part. Participants' data confidentiality was rigorously maintained, with all data anonymised before analysis to protect identities.

3.3.2 Participants

The sample size (n = 16) was informed by previous work examining training-induced adaptations in vastus lateralis motor-unit behaviour using an identical 4-week unilateral force-accuracy training protocol (Ely et al., 2022). Ely et al. (2022) demonstrated significant improvements in force-control accuracy and reductions in motor-unit discharge

variability with ten young healthy participants. Given that the present study involved older adults—a population characterised by greater inter-individual variability—a slightly larger sample (n = 16) was considered appropriate to detect comparable neural adaptations while accounting for expected variance.

3.3.2.1 Eligibility

Sixteen volunteers, comprising eight males and eight females, were recruited from the community using several methods such as flyers, social media ads, and direct outreach. Nineteen individuals were screened, and three were excluded due to not meeting the inclusion criteria or medical contraindications. Their eligibility for participation was assessed based on certain inclusion and exclusion criteria.

Inclusion criteria required individuals to be:

- Aged 65 to 85 years,
- Free from neurological or musculoskeletal disorders,
- Not engaged in structured exercise in the past six months.

Exclusion criteria included:

- Cardiovascular, respiratory, or metabolic disease (e.g., diabetes), uncontrolled blood pressure,
- Medication use affecting neuromuscular function (e.g., corticosteroids),
- BMI <18 or >35 kg/m²,
- Recent steroid treatment, malignancy, or chronic kidney disease,
- Any other medical condition deemed by the investigators to compromise safety or data integrity.

This age range and health profile were selected to ensure a homogeneous, high-functioning older population capable of safely completing the neuromuscular assessments.

3.3.3 Study overview

This study was conducted as a within-subject, split-body design to evaluate the effects of low-intensity FAT on neuromuscular and functional outcomes in healthy older adults. The primary outcomes were MUDR, MUDR variability, FS, maximum voluntary contraction (MVC), and sinusoidal force-tracking accuracy (FTA). Secondary outcomes included jump power, balance, general mobility (TUG, 4MWT, 5xSTS), grip strength, and dexterity.

The trial was carried out over a 24-month period, with assessments conducted at baseline, immediately post-intervention, and at 2-week and 4-week follow-up time points to evaluate retention. All participants performed the FAT intervention using their right leg (right legs were dominant in all), while the left leg remained untrained to allow for within-subject comparison. Each training session involved six isometric sinusoidal force-tracking contractions at 10%, 25%, and 40% of the participant's MVC. These intensities were selected to emphasise neural activation without inducing muscular hypertrophy, consistent with prior FAT protocols (Ely et al., 2022). All testing procedures were conducted bilaterally to assess both trained and untrained limbs.

3.3.3.1 Screening visit

Individuals who showed interest in the study were invited for a screening visit. During this visit, eligibility criteria were confirmed through a series of assessments, including a comprehensive review of medical history, a physical examination, and a blood sample to evaluate health parameters such as liver and kidney function. In addition, a heart assessment was performed, including an electrocardiogram (ECG) to monitor heart activity and check blood pressure.

These assessments involved collecting demographic data, including age, sex, height, weight, and BMI. The screening visit also entailed obtaining informed consent, ensuring

participants fully understood the objectives and procedures of the study. Potential participants were encouraged to ask questions, and any concerns were addressed before proceeding. Those who met the inclusion criteria and passed the exclusion criteria were then scheduled for baseline assessments.

3.3.3.2 Baseline assessment

Baseline assessments were conducted at the beginning of the study. Participants were instructed to attend the laboratory following a 10-hour fast, approximately at 9 am (± 1 h). Primary outcome measures were evaluated using validated and reliable tools, including MVC, balance, neuromuscular function, and HDsEMG. Secondary outcomes encompassed measures of general functional and physical activity levels. Each assessment took place in a controlled environment under the supervision of trained personnel, adhering to standardised protocols to minimise variability. All equipment used during the assessments was calibrated prior to each session to ensure the accuracy and reliability of the measurements.

3.3.3.3 Intervention

The intervention was applied unilaterally and focused on the knee extensor muscle of the right leg. The programme consisted of three weekly sessions lasting approximately thirty minutes over four weeks. During these training sessions, participants were instructed to follow a force tracing of a sinusoidal wave displayed on the monitor in front of them. Each training session involved two contractions at 10%, 25%, and 40% of their MVC in a randomised order. The number of oscillations (either 6, 8, or 10) and the amplitude (either ±2%, ±4%, or ±8%) of the sinusoidal waves differed from those used in the assessment visits (Figure 3.1). Contractions lasted between 20 and 30 seconds, depending on contraction intensity, and were separated by a 60-second rest period. The training regimen

was individualised based on baseline MVC, with each participant beginning at a randomly assigned intensity level suitable for their strength. Trained individuals supervised each session to ensure that participants adhered to the protocol and performed the exercises with the correct technique. Adherence to the intervention was excellent, with all participants completing 100% of the scheduled training sessions. Compliance was monitored through regular researcher check-ins and participant-maintained activity logs to ensure fidelity to the protocol throughout the intervention period.

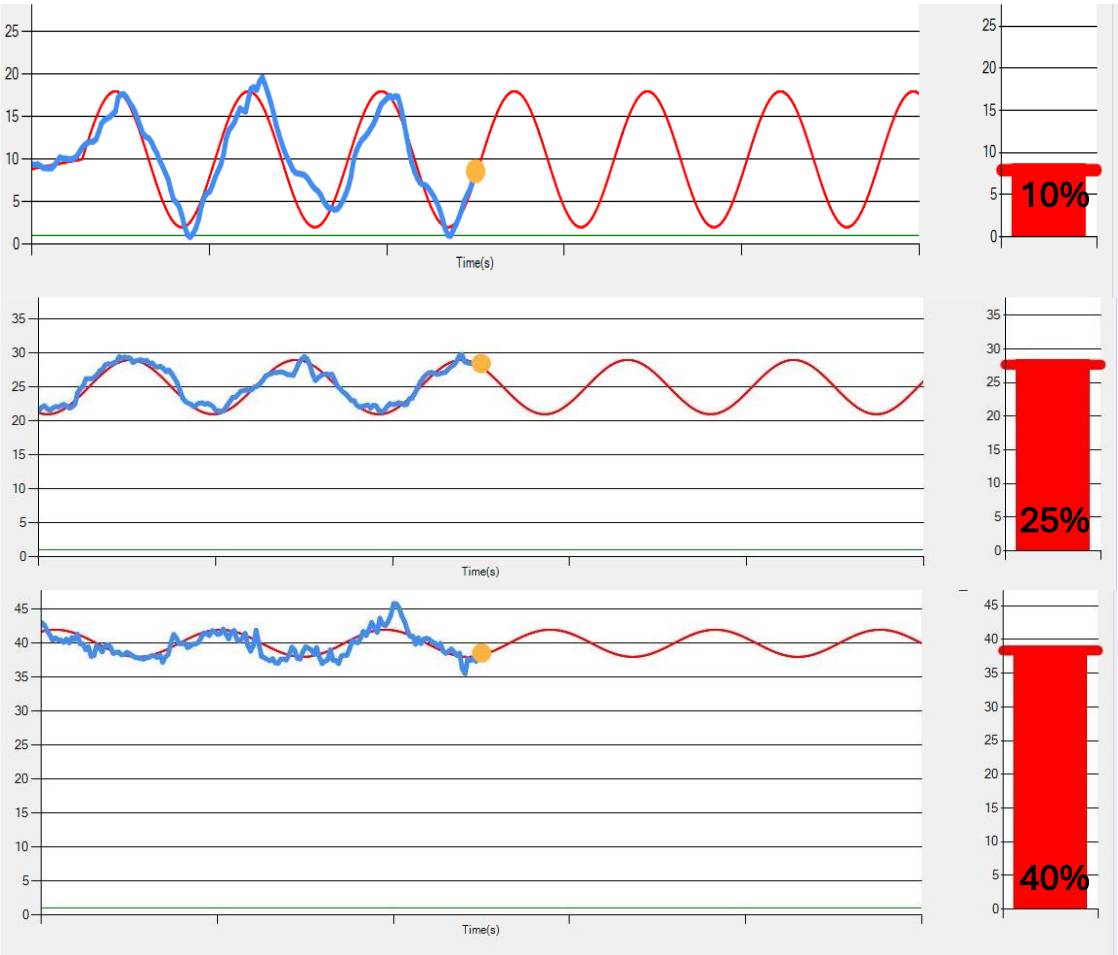


Figure 3.1Example traces of force target (red) and achieved force (blue) at different contraction levels.

3.3.3.4 Post-intervention assessment

Upon completing the intervention, participants underwent a post-intervention assessment (week 4) and two follow-up evaluations (weeks 6 and 8). These assessments were conducted under conditions identical to the baseline to evaluate any changes in the primary and secondary outcome measures that could be attributed to the intervention. In addition to the primary assessments, adherence to the intervention protocol and any reported deviations during the study period were recorded (Figure 3.2).

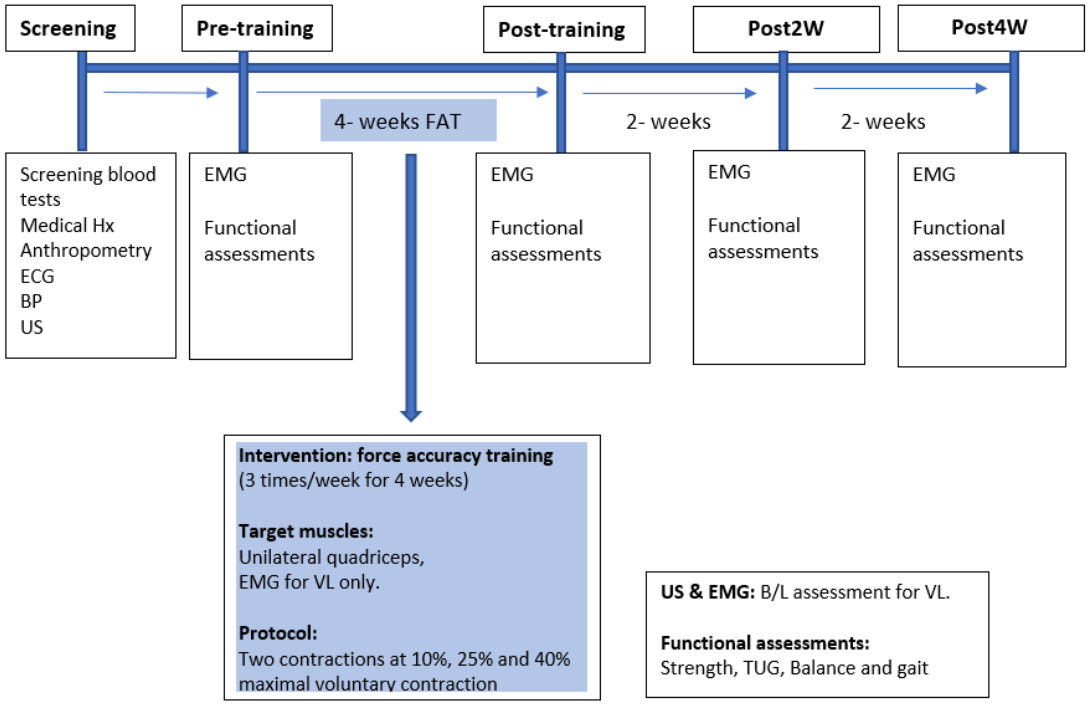


Figure 3.2 Training protocol

FAT: Force accuracy training; ECG: Electrocardiogram; BP: Blood pressure; US: Ultrasound scanning; EMG: Electromyography; B/L: Bilateral; VL: Vastus lateralis muscle; TUG: Timed Up and Go tests.

3.3.4 Measurable endpoints

3.3.4.1 Power

A countermovement jump test was conducted to assess overall lower-limb power. A BTS G-sensor (BTS Bioengineering S.p.A., Milan, Italy) was positioned around the participant's

waist and secured with a belt to the S1 vertebra. The G-sensor was connected via Bluetooth to G-Studio (version 3.3.22.0). The jump was demonstrated before the participant executed a practice jump. This jump required the participant to stand with feet shoulder-width apart, hands on hips, and to bend down to a 90-degree knee angle before springing upward and landing upright. The participant performed three jumps, with a 30-second break between each. The jump with the highest maximum power was recorded for analysis, including take-off speed and jump height parameters.

3.3.4.2 Gait and balance

The Timed Up and Go test (TUG) was used to assess overall mobility and function (Podsiadlo and Richardson, 1991). Participants sat in a chair without armrests, and a BTS G-sensor (BTS S.p.A., Milan, Italy) was placed on their L2 vertebra. An obstacle was positioned three metres in front of the chair. Participants were instructed to stand from the chair without using their hands, walk as quickly as possible around the obstacle, return to the chair, then turn and sit again without using their hands. The method was demonstrated to the participants before they made two individual attempts. The shortest time was recorded using G-Studio (BTS S.p.A.) and used for analysis.

The 4 Metre Walk Test (4MWT) is a walking speed test that assesses physical performance and functional limitations (Nguyen et al., 2022). Participants were instructed to stand with both feet behind the first mark (0M). They were then asked to walk at their usual pace. Start timing with a stopwatch once one foot crosses the first mark (0M) and stop timing when one foot crosses the final mark (4M). The participants were instructed to perform the test twice, and the quickest time was used for analysis.

The 5x Sit-To-Stand Test is commonly abbreviated as 5XSST. It assesses functional lower limb strength, transitional movements, balance, and fall risk in older adults (Melo et al., 2019). The 5XSST score is determined by the time (in seconds) it takes for an individual to shift from sitting to standing and back to sitting five times. Participants were asked to sit on the chairs and relax their backs. Additionally, they were instructed to cross their arms over their chests. The test takers were then prompted to complete the sit-to-stand sequence five times as quickly as possible, starting at the count of "go," without resting their backs or legs on the chairs between repetitions. Timing began when the examiner said "start" and ended when the individuals' buttocks touched the seats of the chairs after the final repetition.

Balance was measured for each leg separately using a Materialise Footscan 1-metre force plate (Materialise, Leuven, Belgium). Subjects stood naturally in the centre of the force plate for 10 seconds to measure the centre of pressure (COP) distance. For single-leg balances, participants were asked to raise their opposite foot at least 5 inches off the floor. They were permitted to use their arms to maintain stability if needed and were instructed to place their foot down if they felt they might fall to avoid injury. Participants received a countdown from 5 to commence the balance recording and were told to raise their foot on 2. This ensured the balancing did not take longer than necessary. Similar to both-leg balance, the single-leg balance was recorded for 10 seconds, and the COP distances moved were measured.

3.3.4.3 Hand grip strength, manual dexterity, and coordination

The peak unilateral handgrip strength was measured using a handgrip dynamometer (T.K.K. A5401, Takei Scientific Instruments, Niigata, Japan). Participants sat at a table,

with the elbow and forearm of the tested arm resting on the table, and the wrist held in a neutral posture whilst gripping the dynamometer. The grip width was adjusted to accommodate each participant's hand. Participants were instructed to squeeze the dynamometer as hard as possible for three seconds and then relax. Following a 30-second rest period between attempts, three measurements were recorded from each arm, and the highest values were used for analysis.

The Grooved Pegboard Test (GPT) is a standardised, timed, manipulative dexterity assessment designed to evaluate fine motor coordination, manual dexterity, and psychomotor speed (Tolle et al., 2020). While the participants were seated at a table with the pegboard placed in front of them, they were instructed to insert key-shaped metal pegs into a board with grooved slots that required precise orientation and hand-eye coordination. Time was recorded from the moment the participants touched the first peg until the last peg was correctly placed.

3.3.4.4 Knee extensor MVC

Knee extensor (KE) strength was assessed with participants seated in a custom-made chair, their hips and knees flexed at 90°, and their legs securely fastened to a force transducer just above the ankle. Participants performed a series of submaximal contractions to familiarise themselves with the equipment and warm up their muscles. Subsequently, they were instructed to complete a maximal isometric contraction while receiving verbal encouragement and visual feedback on force. This process was repeated three times with 60-second rest periods in between. The best effort was recorded as the MVC.

3.3.4.5 Force steadiness and force tracking accuracy

FS, defined as the coefficient of variation for force, was assessed by having participants maintain a submaximal isometric contraction on a target line displayed on a monitor at 25% of their previously obtained MVC. The force signals were low-pass filtered at 20 Hz using a fourth-order Butterworth digital filter. Each contraction was repeated at least 4 times, with 30 seconds of rest between repetitions. Each isometric contraction was held for 10 seconds, during which the signal was recorded to evaluate variability in force output. The FS during the recorded isometric contraction was measured for each contraction and averaged across all contractions. Each force assessment during the four sessions (baseline, post, 2 weeks post, and 4 weeks post) was normalised to the same-day MVC score. The force signals were presented in real-time using Spike2 software (v9.06, Cambridge Electronic Design, UK), and data were recorded simultaneously from the force transducer for offline analysis. HD-sEMG was recorded simultaneously during each of these contractions as described below.

FTA refers to the correlation coefficient (CC) between the target force path (a pre-defined sinusoidal wave) and the actual force generated (Figure 3.3). This method was utilised to assess how well the participant could synchronise the timing and shape of their force production with the oscillating target. Participants were instructed to perform a series of sinusoidal force-tracking tasks using OT Bioelettronica software (Torino, Italy), set at 25% of their same-day MVC, to evaluate FTA. Prior to the actual assessment, a familiarisation trial was conducted. Each contraction included eight oscillations with a fixed amplitude (±4%) over a 30-second period. To ensure a gradual transition, a 10-second ramp phase was incorporated before and after the oscillating portion, allowing the force to rise and fall

smoothly to and from the target intensity. The contractions were exported and processed using a custom-written script in MATLAB (v 2023 b, IBM).

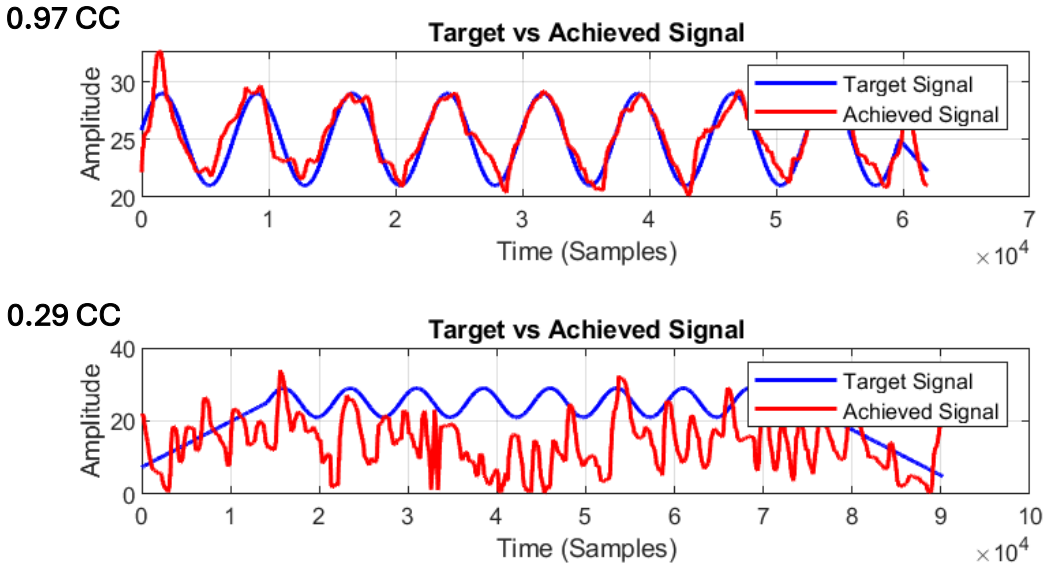


Figure 3.3 Example of force tracking accuracy performance. The well-tracked trial demonstrated a high correlation with the target waveform (CC = 0.97), while the poorly tracked trial showed a substantially lower correlation (CC = 0.29). CC: correlation coefficient

3.3.4.6 Electromyography (EMG)

HDsEMG array (64 electrodes, 13 × 5, 8 mm, I.E.D., GR08MM1305, OT Bioelettronica, Inc., Turin, Italy) was used bilaterally on each VL. Before using HDsEMG, the hair on the thighs was shaved and cleaned with 70% ethanol. The HDsEMG electrodes were secured with flexible tape to stabilise them during the assessment visits. A ground electrode (WS2, OTBioelettronica, Turin, Italy) was placed around the ankle of the tested leg. HDsEMG signals were acquired in a monopolar configuration, amplified (× 256), with filtering set between 10-500 Hz, and digitally converted at 2000 Hz using a 16-bit wireless amplifier (Sessantaquattro, OTBioelettronica, Turin, Italy). Data was visualised in real time using the OTBioLab+ software (v1.3.2, OT Bioelettronica) and saved for offline analysis.

The collected HDsEMG data were converted into MATLAB files, each representing one contraction. Although participants completed six submaximal contractions, only one trial per protocol, chosen based on the smoothness of its force profile, was used for analysis. The monopolar HDsEMG signals were band-pass filtered between 20 and 500 Hz, and subsequently decomposed offline into MU spike trains using the convolutive kernel compensation algorithm (Holobar and Zazula, 2007, Holobar et al., 2014). The analysis concentrated on the HD-sEMG data from the middle contractions (contractions 3 and 4 out of six) at 25% MVC. To enhance the likelihood of sampling the same MUs over time, the HDsEMG electrode positions were accurately measured with respect to the femur's greater trochanter and lateral epicondyle during the baseline session. MUs with a pulse-to-noise ratio (PNR) ≥ 30 dB were included in the analysis. Manual editing of consecutive firings was conducted to improve decomposition accuracy (Del Vecchio et al., 2020). The main MU outcomes were:

- MUDR: mean firing frequency during a 10-second plateau at 25% MVC,
- MUDR variability: coefficient of variation of inter-spike intervals.

3.3.5 Statistical analysis

To evaluate time- and limb-based effects while accounting for repeated measurements and nested MU data, linear mixed-effects models (LMMs) were implemented using RStudio (v4.4.3) with the lme4 package (Bates et al., 2015). Models included fixed effects of time, leg, and the time × leg interaction where appropriate. Time was modelled with both linear and quadratic terms to account for non-linear trends in training adaptation and detraining effects, as neuromuscular changes are often not strictly proportional over time (e.g., initial rapid improvements followed by plateauing or decline). Random slopes were included where supported by model fit to capture inter-individual variability in trajectories.

For outcome measures that were assessed bilaterally (e.g., FS, MVC, and MUDR), leg was included as a fixed factor to examine asymmetry and potential cross-limb effects. However, for assessments that inherently involve both limbs or global function (e.g., TUG, 4MWT), the leg was not included as a factor, as these measures do not permit within-subject limb comparisons.

Post-hoc comparisons were conducted using the emmeans package (Lenth and Lenth, 2018), and all results are presented as Estimated Marginal Means (EMMs) with 95% confidence intervals. Statistical significance was set at $p < 0.05$. This analytical approach provides a flexible framework for detecting both linear and non-linear adaptations over time, while accounting for individual variability and hierarchical data structure.

Individual participant data and group trends were visualised using spaghetti plots (connected line plots). Each coloured line represents an individual participant's data across time points, with black diamonds and error bars indicating group mean ± standard deviation. This approach allows the depiction of both inter-individual variability and group-level changes over time. The same graphical format is used consistently throughout Chapters 4 and 5 to illustrate functional, neuromuscular, and MU outcomes.

3.4 Results

3.4.1 Participant characteristics

All participants (n = 16; 8 females) completed the entire protocol, which included training and detraining assessments. Table 3.1 provides a summary of the baseline demographic and physiological characteristics.

Table 3.1 Participants characteristics (n = 16; 8 female)

Age (years)	73.8 (5.1)
Height (cm)	166.7 (6.8)
Weight (kg)	73.9 (10.4)
BMI (kg/m2)	26.6 (2.7)
Right VL CSA (cm2)	17.7 (3.7)
Left VL CSA (cm2)	17.3 (2.5)

Data shown as mean (standard deviation). VL CSA was obtained at baseline. *Abbreviations*: *BMI, body mass index; VL CSA, vastus lateralis cross-sectional area.*

3.4.2 Functional measures

3.4.2.1 Jump power

For jump power, there was a significant linear (p = .015) and quadratic (p = .009) effect of time (Figure 3.4A). EMMs confirmed significant increases from Pre to Post (p = 0.005) and Pre to Post2W (p = 0.003).

Table 3.2 Jump power (JP)

Time	Mean (KW)	SD	95% CI	Change vs. Pre
Pre	2.30	0.45	[2.06, 2.54]	—
Post	2.60	0.47	[2.35, 2.85]	+13 % ↑ (p = 0.005)
Post2W	2.65	0.46	[2.40, 2.90]	+15 % ↑ (p = 0.003)
Post4W	2.55	0.45	[2.31, 2.79]	+11 % (ns)

Abbreviations: *KW, kilowatts; SD, standard deviation; CI, confidence intervals.*

3.4.2.2 Timed up-and-go

There was a significant linear decrease in TUG performance over time (p = 0.027) (Figure 3.4B), although EMMs did not show significant differences across individual timepoints (all p > 0.11). There was no main effect of time for the 4MWT (p > 0.218) or the 5 STS (p > 0.08) (Figures 3.4C and 3.4D, respectively).

Table 3.3 Timed up-and-go (TUG), 4-meters walk test (4MWT) and 5 sit-to-stand test (5STS)

Task	Time	Mean (s)	SD	95% CI	Change vs. Pre
TUG	Pre	8.7	1.5	[7.90, 9.50]	—
	Post	8.2	1.4	[7.55, 9.05]	−5 % ↓ (ns)

	Post2W	8.1	1.5	[7.40, 9.00]	−6 % ↓ (ns)
	Post4W	8.1	1.6	[7.35, 9.05]	−6 % ↓ (ns)
4MWT	Pre	2.9	0.4	[2.69, 3.11]	—
	Post	2.8	0.4	[2.59, 3.01]	−3 % (ns)
	Post2W	2.9	0.4	[2.69, 3.11]	0 % (ns)
	Post4W	2.9	0.4	[2.69, 3.11]	0 % (ns)
5STS	Pre	9.1	1.7	[8.19, 10.01]	—
	Post	8.7	1.6	[7.85, 9.55]	−4 % (ns)
	Post2W	8.6	1.5	[7.80, 9.40]	−5 % (ns)
	Post4W	8.8	1.6	[7.95, 9.65]	−3 % (ns)

Abbreviations: *s, seconds; SD, standard deviation; CI, confidence intervals.*

3.4.2.3 Balance, dexterity, and general function

There was a significant quadratic leg x time interaction ($p = 0.049$) for single-leg balance, indicating a differential response between legs (Figure 3.5A). There was no significant main effect of time ($p=0.233$) or leg ($p=0.062$). EMMs revealed that a progressive decrease in distance moved can explain the interaction in the exercised leg, decreasing from Pre to Post ($p < 0.001$), Pre to Post2W ($p < 0.001$), and Pre to Post4W ($p = 0.007$), whereas there were no significant changes across time in the control leg (all $p>0.24$).

For handgrip strength (Figure 3.5B), there were no significant interactions between hand (right and left) and time (both $p>0.73$). There were no main effects of time (both $p>0.36$), but there was a significant difference across limbs, with the right GS consistently stronger than the left, at all timepoints (all $p<0.004$).

For the grooved pegboard test (Figure 3.5C), there was no hand x time interaction (both $p>0.7$) and no main effect of time (both $p>0.32$). There was a main effect of hand ($p=0.028$), with pairwise comparisons revealing a lower time in the right hand at Pre, Post, and Post4W (all $P<0.05$).

Table 3.4 Single-leg balance (SLB)

Group	Time	Mean (mm)	SD	95% CI	Change vs. Pre
Control	Pre	300	120	[236.1, 363.9]	—
	Post	280	115	[218.7, 341.3]	−7 % (ns)
	Post2W	290	118	[227.1, 352.9]	−3 % (ns)
	Post4W	295	120	[231.1, 358.9]	−2 % (ns)
Exercise	Pre	310	130	[240.7, 379.3]	—
	Post	240	110	[181.4, 298.6]	−23 % ↓ ($p < 0.001$)
	Post2W	235	105	[179.1, 290.9]	−24 % ↓ ($p < 0.001$)
	Post4W	255	115	[193.7, 316.3]	−18 % ↓ ($p = 0.007$)

Abbreviations: *mm, millimetre; SD, standard deviation; CI, confidence intervals.*

Table 3.5 Handgrip Strength (GS)

Group	Time	Mean (kg)	SD	95% CI	Change vs. Pre
Left (non-dominant)	Pre	28.0	5.8	[24.91, 31.09]	—
	Post	28.3	5.6	[25.32, 31.28]	+1 % (ns)
	Post2W	28.2	5.7	[25.16, 31.24]	0 % (ns)
	Post4W	28.0	5.8	[24.9, 31.09]	0 % (ns)
Right (dominant)	Pre	31.5	6.0	[28.30, 34.70]	—
	Post	31.7	5.9	[28.56, 34.84]	+1 % (ns)
	Post2W	31.6	6.0	[28.40, 34.80]	0 % (ns)
	Post4W	31.8	6.1	[28.55, 35.05]	+1 % (ns)

Abbreviations: *kg, kilogram; SD, standard deviation; CI, confidence intervals.*

Table 3.6 Grooved pegboard test

Group	Time	Mean (s)	SD	95% CI	Change vs. Pre
Left (non-dominant)	Pre	85.0	12.0	[78.61, 91.39]	—
	Post	83.0	11.5	[76.87, 89.13]	−2 % (ns)
	Post4W	84.0	11.8	[77.71, 90.29]	−1 % (ns)
Right (dominant)	Pre	79.0	11.0	[73.14, 84.86]	—
	Post	78.0	10.8	[72.25, 83.75]	−1 % (ns)
	Post4W	78.5	10.9	[72.69, 84.31]	−1 % (ns)

Abbreviations: *s, seconds; SD, standard deviation; CI, confidence intervals.*

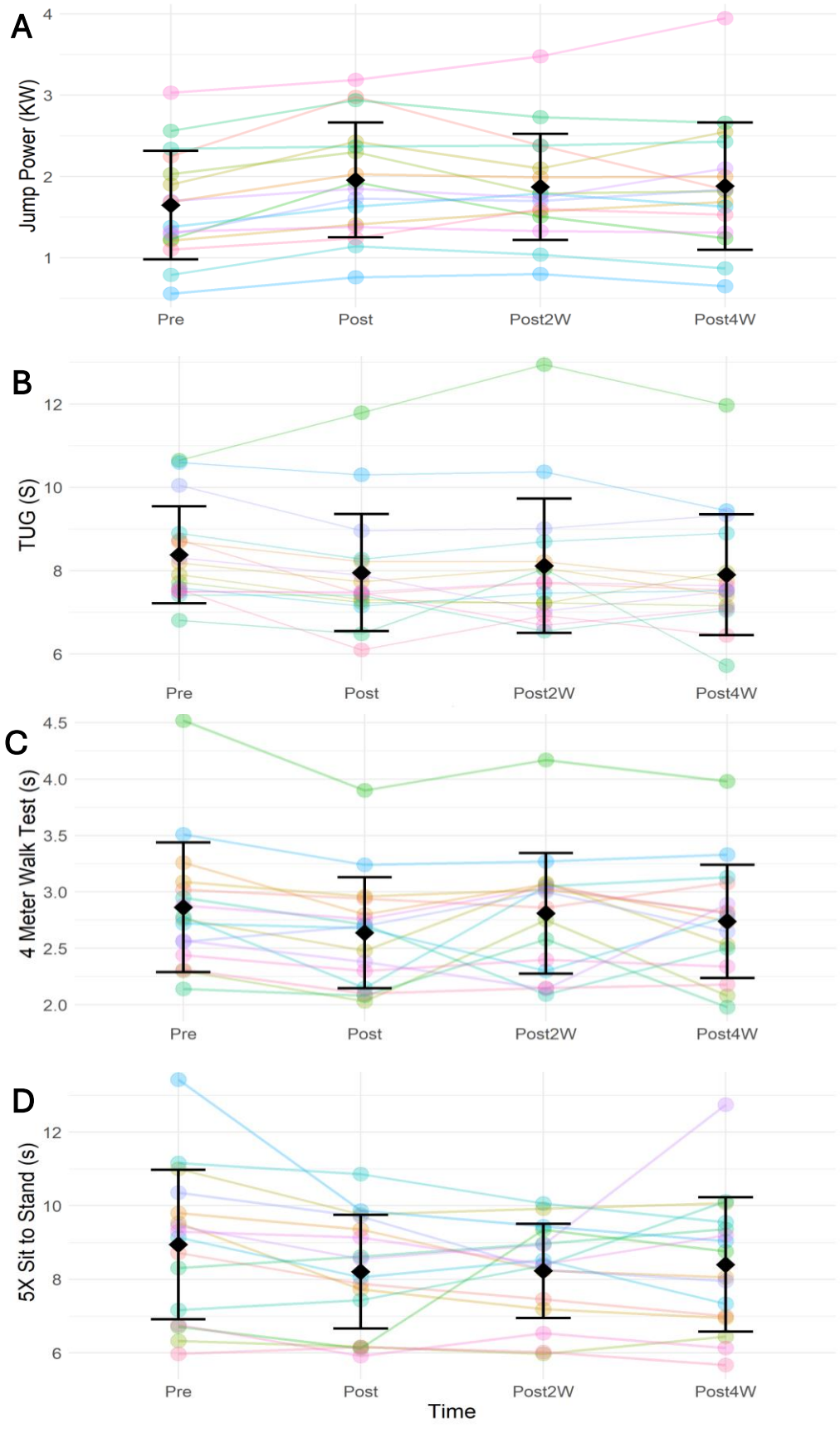

A
Jump Power (KW)
4
3
2
1
Pre
Post
Post2W
Post4W
B
TUG (S)
12
10
8
6
Pre
Post
Post2W
Post4W
C
4 Meter Walk Test (s)
4.5
4.0
3.5
3.0
2.5
2.0
Pre
Post
Post2W
Post4W
D
5X Sit to Stand (s)
12
10
8
6
Pre
Post
Post2W
Post4W
Time

Figure 3.4 (A). Jump power (B). Timed up and go, (C). 4 Meter walk test, and (D). Five times sit to stand at Pre, Post, Post 2-weeks and Post 4-weeks intervention. TUG, Timed up and go; KW, Kilo Watts; S, Seconds. Black diamonds represent group means, black error bars indicate standard deviations (SD), and coloured circles show individual participant values, with lines connecting data from the same participant across time points.

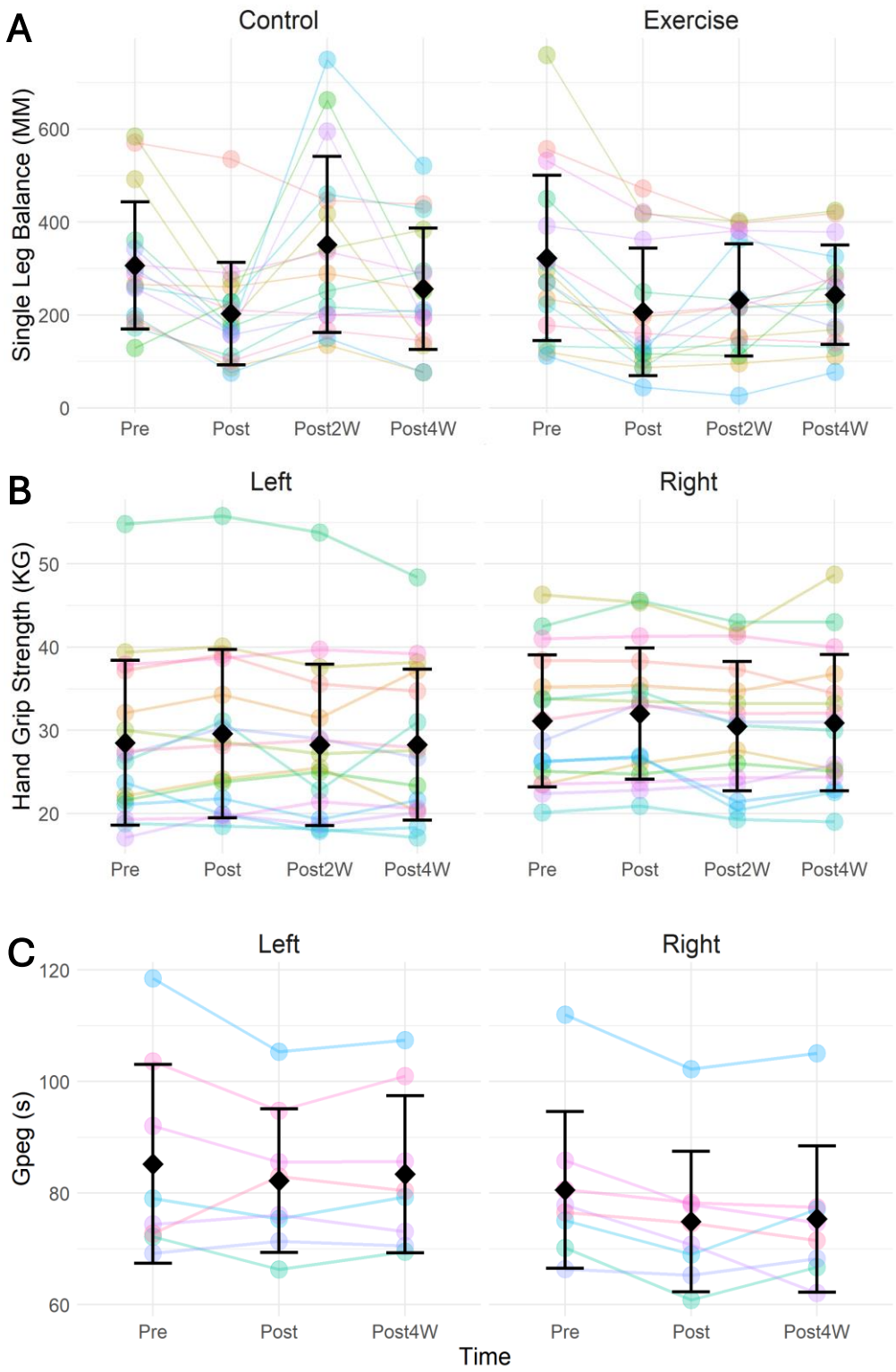


Figure 3.5 (A). Single leg balance (B). Hand grip strength, and (C). Grooved pegboard test at Pre, Post, Post 2 weeks and Post 4 weeks intervention. MM, Millimetre; KG, Kilogram; Gpeg, Grooved Pegboard Test; S, Seconds. Control and exercise groups are displayed separately where applicable. Black diamonds represent group means, black error bars

indicate standard deviations (SD), and coloured circles show individual participant values, with lines connecting data from the same participant across time points.

3.4.2.4 Knee extensors MVC

For KE MVC, there was no significant time × leg interaction (both $p > 0.19$). There was a significant quadratic effect of time ($p = 0.027$), consistent with a non-linear change pattern (Figure 3.6A). There was also a significant effect of leg, higher in the exercise compared to the control leg ($p = 0.012$). EMMs showed a significant increase in MVC from Pre to Post ($p = 0.005$), and from Pre to Post2W ($p = 0.009$), with no further significant adaptations.

Table 3.7 Knee extensors maximum voluntary contraction (MVC)

Group	Time	Mean (N)	SD	95% CI	Change vs. Pre
Control	Pre	280	50	[253, 306]	—
	Post	300	52	[272, 327]	+7 % ↑ (p = 0.005)
	Post2W	305	53	[276, 333]	+9 % ↑ (p = 0.009)
	Post4W	295	51	[267, 322]	+5 % (ns)
Exercise	Pre	285	52	[257, 312]	—
	Post	310	54	[281, 338]	+9 % ↑ (p = 0.005)
	Post2W	315	55	[285, 344]	+11 % ↑ (p = 0.009)
	Post4W	305	53	[276, 333]	+7 % (ns)

Abbreviations: *N, Newtons; SD, standard deviation; CI, confidence intervals.*

3.4.2.5 Force steadiness and sinewave tracking

For KE FS, there was no significant time × leg interaction (both $p > 0.36$). There was a significant main effect of time, with both linear ($p < 0.001$) and quadratic ($p = 0.010$) trends (Figure 3.6B). A significant main effect of leg was also found ($p = 0.001$), with the trained leg showing lower KE FS values than the control leg. EMMs showed a significant decrease in FS from Pre to Post ($p < 0.001$), from Pre to Post2W (< 0.001), and from Pre to Post4W ($p < 0.001$).

When assessing the sinewave task, a linear mixed-effects model revealed both a significant linear increase ($p < 0.001$) and a significant quadratic change ($p = 0.004$) in the CC of KE during the sinewave task. There was an effect of leg, with the trained showing higher values overall ($p < .001$), but there was no significant leg x time interaction (both $p > 0.2$). EMMs indicated significant increases from Pre to Post ($p = .0003$), Pre to Post2W ($p = .0002$), and Pre to Post4W ($p = .0011$). There was no significant difference between Post2W and Post4W, indicating a plateau following initial gains (Figure 3.6C).

Table 3.8 Knee extensors force steadiness (FS)

Group	Time	Mean (CoV)	SD	95% CI	Change vs. Pre
Control	Pre	0.027	0.004	[0.025, 0.029]	—
	Post	0.024	0.004	[0.022, 0.026]	−11 ↓ ($p < 0.001$)
	Post2W	0.023	0.004	[0.021, 0.025]	−15 ↓ ($p < 0.001$)
	Post4W	0.023	0.004	[0.021, 0.025]	−15 ↓ ($p < 0.001$)
Exercise	Pre	0.024	0.004	[0.022, 0.026]	—
	Post	0.020	0.003	[0.018, 0.022]	−17 ↓ ($p < 0.001$)
	Post2W	0.019	0.003	[0.017, 0.021]	−21 ↓ ($p < 0.001$)
	Post4W	0.019	0.003	[0.017, 0.021]	−21 ↓ ($p < 0.001$)

Abbreviations: CoV*, coefficient of variation; SD, standard deviation; CI, confidence intervals.*

Table 3.9 Knee extensors force tracking accuracy (FTA)

Group	Time	Mean (CC)	SD	95% CI	Change vs. Pre
Control	Pre	0.720	0.050	[0.693, 0.747]	—
	Post	0.750	0.045	[0.726, 0.774]	+4 % ↑ (p = 0.0003)
	Post2W	0.760	0.045	[0.736, 0.784]	+6 % ↑ (p = 0.0002)
	Post4W	0.760	0.045	[0.736, 0.784]	+6 % ↑ (p = 0.0011)
Exercise	Pre	0.730	0.050	[0.703, 0.757]	—
	Post	0.780	0.045	[0.756, 0.804]	+7 % ↑ (p = 0.0003)
	Post2W	0.790	0.045	[0.766, 0.814]	+8 % ↑ (p = 0.0002)
	Post4W	0.790	0.045	[0.766, 0.814]	+8 % ↑ (p = 0.0011)

Abbreviations: *CC, correlation coefficient; SD, standard deviation; CI, confidence intervals.*

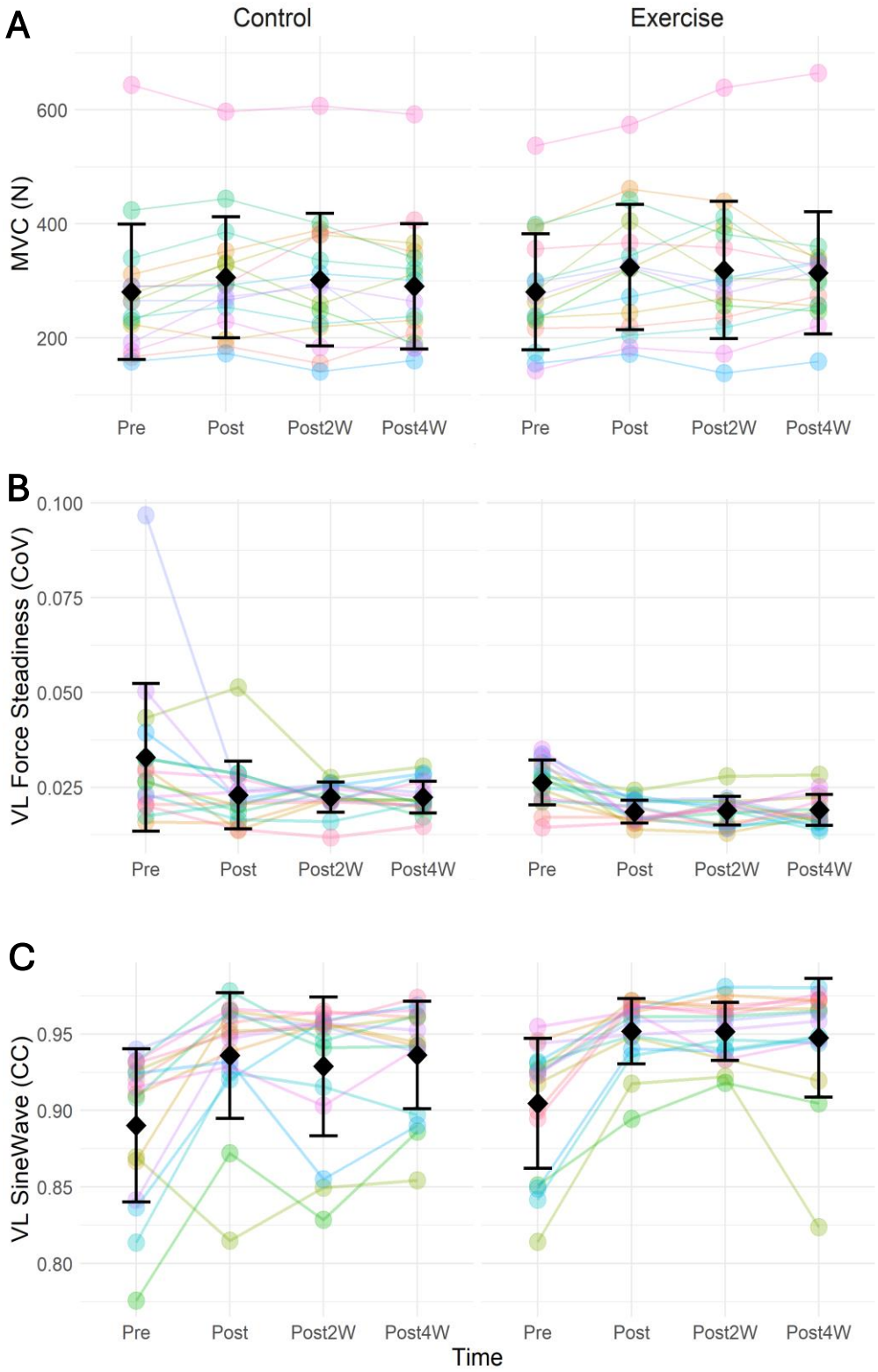


Figure 3.6 (A). Knee extensors MVC; (B). Force steadiness and (C). Sinewave task of control and exercise limbs at Pre, Post, Post 2-weeks and Post 4-weeks intervention. VL,

Vastus Lateralis; MVC, maximum voluntary contraction; N, Newtons; CoV, Coefficient of Variation; CC, Correlation Coefficient. Control and exercise groups are displayed separately where applicable. Black diamonds represent group means, black error bars indicate standard deviations (SD), and coloured circles show individual participant values, with lines connecting data from the same participant across time points.

3.4.3 Electromyography (EMG)

For VL MUDR (n=9), a linear mixed-effects model revealed a significant linear interaction ($p < 0.001$), a significant effect of leg ($p = 0.001$), and a significant linear effect of time ($p = 0.002$). EMMs indicated a significant decrease in the control leg only from Pre to Post4W, with no further differences in either leg. MUDR was significantly lower in the control leg at Post2W ($p < 0.001$) and Post4W ($p < 0.001$) (Figure 3.7A).

For VL MUDR variability (n=9), there was no significant interaction (both $p > 0.055$). There was no significant effect of time (both $p > 0.08$), but there was a significant effect of leg ($p<0.001$). EMMs showed significantly higher MUDR variability in the control leg compared to the exercise leg (Figure 3.7B).

Table 3.10 Vastus lateralis (VL) motor unit discharge rate (MUDR)

Group	Time	Mean (pps)	SD	95% CI	Change vs. Pre
Control	Pre	12.0	1.8	[10.62, 13.38]	—
	Post	11.6	1.9	[10.14, 13.06]	−3 % (ns)
	Post2W	10.8	1.7	[9.49, 12.11]	−10 % ↓ ($p < 0.001$)
	Post4W	10.2	1.6	[8.97, 11.43]	−15 % ↓ ($p < 0.001$)
Exercise	Pre	12.4	1.9	[10.94, 13.86]	—
	Post	12.3	1.8	[10.92, 13.68]	0 % (ns)
	Post2W	12.2	1.8	[10.82, 13.58]	−2 % (ns)
	Post4W	12.1	1.8	[10.72, 13.48]	−3 % (ns)

Abbreviations: *pps, pulses per second; SD, standard deviation; CI, confidence intervals.*

Table 3.11 Vastus lateralis (VL) motor unit discharge rate (MUDR) variability

Group	Time	Mean (CoV)	SD	95% CI	Change vs. Pre
Control	Pre	0.28	0.05	[0.242, 0.318]	—
	Post	0.27	0.05	[0.232, 0.308]	−4 % (ns)
	Post2W	0.28	0.05	[0.242, 0.318]	0 % (ns)

	Post4W	0.27	0.05	[0.232, 0.308]	−4 % (ns)
Exercise	Pre	0.22	0.04	[0.189, 0.251]	—
	Post	0.21	0.04	[0.179, 0.241]	−5 % (ns)
	Post2W	0.21	0.04	[0.179, 0.241]	−5 % (ns)
	Post4W	0.22	0.04	[0.189, 0.251]	0 % (ns)

Abbreviations: CoV*, coefficient of variation; SD, standard deviation; CI, confidence intervals.*

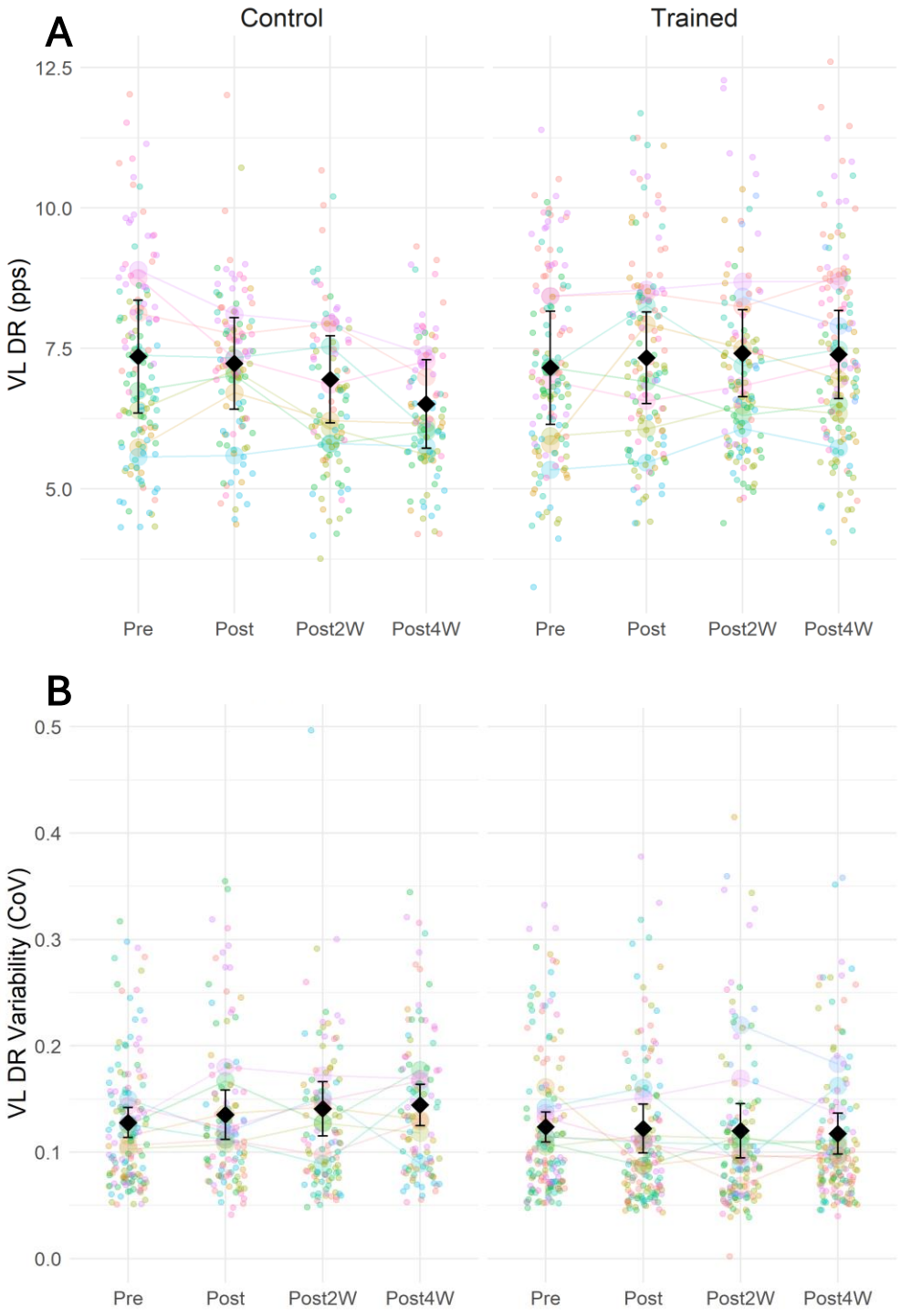


Figure 3.7 (A). VL discharge rate; and (B). VL discharge rate variability of control and exercise muscle at Pre, Post, Post 2-weeks and Post 4-weeks intervention. VL, Vastus Lateralis; DR, discharge rate; pps, pulse per second; CoV, coefficient of variation. Control and exercise groups are displayed separately where applicable. Black diamonds and error bars represent estimated marginal means and 95% CI from model outputs. Large, coloured circles show individual participant means, with lines connecting data from the same

participant across time points, and small coloured circles show individual motor unit values, colour-coded to participant.

3.5 Discussion

This study investigated the effects of a 4-week unilateral low-intensity FAT programme on the neuromuscular function of the VL muscle in healthy older adults. The primary findings demonstrate that FAT elicited significant bilateral improvements in strength and neuromuscular control, with evidence of functional enhancement and retention of gains following detraining. These results highlight FAT as a promising low-intensity intervention for maintaining neuromuscular health in ageing populations.

In addition to functional outcomes, the present study offers novel insights into neural adaptations, particularly regarding MU behaviour. The preservation of MUDR and reduced discharge variability represent key neurophysiological changes, rarely captured in low-intensity training studies. These findings strengthen the mechanistic understanding of FAT's effects and underscore its role in preserving neuromuscular precision with ageing.

The observed increase in VL MVC aligns with previous research demonstrating neural contributions to early strength gains, albeit in younger people (Del Vecchio et al., 2019). While there was no significant time × leg interaction, both limbs exhibited similar improvements over time, supported by a significant quadratic time effect. This indicates bilateral strength gains and strongly suggests CE, where unilateral training induces neural adaptations in the contralateral limb (Green and Gabriel, 2018b, Hendy and Lamon, 2017, Manca et al., 2017b). The trained limb remained stronger overall, as indicated by a main effect of leg. Yet, improvements in the untrained limb reinforce FAT's potential to drive systemic neuromuscular adaptations beyond local effects.

While traditional resistance training relies heavily on muscle hypertrophy, low-intensity isometric interventions like FAT likely enhance strength via increased MU recruitment efficacy and DR modulation, mechanisms particularly relevant for older adults facing anabolic resistance (Phillips et al., 2017b). These neural mechanisms align with CE literature, suggesting increased corticospinal excitability and interhemispheric facilitation as drivers of contralateral improvements (Calvert and Carson, 2022).

Improvements in sinusoidal FTA were observed in both limbs, supported by a significant main effect of time without interaction. This bilateral enhancement implies central neural adaptations that improve FS and motor control, critical for mobility and fall prevention (Enoka and Farina, 2021, Carville et al., 2007, Seynnes et al., 2005). Increased force variability is linked to impaired mobility in older adults (Chung-Hoon et al., 2016, Mani et al., 2018), and thus reductions observed here have clear functional relevance.

This study is one of the first to use HDsEMG to longitudinally track individual MU adaptations to low-intensity training in healthy older adults. The MUDR data revealed a significant time × leg interaction: DRs were maintained in the trained VL, whereas they declined in the untrained control limb over the follow-up period. This decline is consistent with age-related reductions in descending neural drive or synaptic efficiency (Piasecki et al., 2016d). Conversely, the maintenance of MUDR in the trained limb likely reflects training-induced improvements in motoneuron excitability (Orssatto et al., 2023).

Additionally, findings indicate that older individuals exhibit marked improvements in DR after training (Kamen and Knight, 2004). These findings align with evidence that training enhances synaptic input and motor neuron output (Del Vecchio et al., 2019), thereby reinforcing the neuroprotective effect of habitual loading on motoneuron function.

The greater stability of DR in the trained leg supports the hypothesis that FAT promotes more consistent and reliable MU output. This is further evidenced by the reduced MUDR variability in the trained VL compared to the control limb, which remained consistently higher. Although variability did not change significantly over time, the lower variability in the exercised muscle indicates improved temporal precision of MU firing, a marker of enhanced neuromuscular control. This precision is particularly important in older adults, who exhibit increased MU discharge variability linked to impaired manual dexterity and reduced force control, and in whom poorer FS is associated with a history of falls (Enoka and Farina, 2021, Tracy et al., 2005a, Kornatz et al., 2005, Carville et al., 2007).

The present findings align with the concept that FAT engages neuroplastic mechanisms within the motoneuron pool to enhance output consistency and responsiveness. In the ageing context, where MU denervation, reinnervation, and altered DRs can impair muscle control (Jones et al., 2022), an intervention that stabilises MU discharge could have clinical relevance even without causing hypertrophy. Furthermore, maintaining MUDR after training and follow-up supports neural retention and highlights FAT's ability to preserve motoneuron excitability over time, as evidenced by training-induced improvements in DR in older adults (e.g., (Orssatto et al., 2023, Kamen and Knight, 2004)).

These adaptations likely contribute to the functional improvements observed in the trained limb, such as increased force accuracy and strength. They may also underpin the partial cross-education effects detected in the untrained VL, as systemic changes in cortical excitability and motor planning may influence bilateral MU behaviour (Calvert and Carson, 2022, Green and Gabriel, 2018a).

While the contralateral limb did not consistently show significant change, trends toward improved neuromuscular control suggest a task-specific CE effect. This aligns with

previous evidence that unilateral isometric training can produce bilateral improvements through centrally mediated mechanisms (Lee and Carroll, 2007b, Carroll et al., 2006a).

Notably, balance performance improved significantly in the exercised limb, with no change in the control limb. This suggests that even in the absence of high mechanical load, FAT can enhance postural control, likely through improved proprioceptive feedback and neural drive to stabilising muscles. This has practical implications for fall prevention strategies in community-dwelling older adults.

The retention of neuromuscular adaptations observed at 2- and 4-weeks post-intervention supports previous findings that neural gains can persist beyond the training period (Taaffe and Marcus, 1997, Clark et al., 2014, Baxter et al., 2024). This highlights FAT as a sustainable and time-efficient method for older adults who may not be able to engage in prolonged exercise regimens.

Although the intervention targeted only one limb, improvements in jump power and functional mobility measures, such as TUG, suggest a generalised benefit potentially linked to central neural adaptations and CE effect. This is further supported by previous evidence that unilateral training can produce systemic improvements, particularly in functional motor tasks (Green and Gabriel, 2018b, Dragert and Zehr, 2013).

Interestingly, no significant improvements were observed in 4MWT or 5xSTS performance. These findings may indicate a ceiling effect in relatively healthy, active older adults or the need for longer or more intense intervention durations to affect habitual gait or endurance-based tasks.

The lack of significant interaction effects in grip strength and grooved pegboard tests supports the specificity of FAT to the trained neuromuscular pathways and highlights the absence of upper limb CE. However, these results also validate the within-subject control

model and emphasise that the improvements observed are likely attributable to the local effects of the intervention.

It is important to acknowledge that the cohort was relatively healthy and active, which may have limited observable improvements in some measures. Future studies should investigate FAT in frailer or mobility-limited populations and explore its capacity for structural adaptations over longer durations.

Importantly, CE effects were clearly evident, with bilateral improvements in strength and neuromuscular control despite training only one limb. This bilateral enhancement is consistent with previous reports of unilateral training inducing contralateral neural adaptations, likely mediated by interhemispheric facilitation, cortical reorganisation, and shared motor networks (Calvert and Carson, 2022, Lee and Carroll, 2007b). Such neuroplastic responses position FAT as a promising low-load intervention for enhancing function and preventing falls in older adults.

Overall, these results confirm that FAT is an effective and well-tolerated intervention capable of enhancing neuromuscular performance in older adults. Taken together, they position FAT as a low-load, neuromuscular-targeted alternative to traditional RET. Unlike high-intensity training, FAT appears to elicit adaptations primarily through neural mechanisms, making it particularly suitable for frail or mobility-limited populations. This neural emphasis highlights FAT's potential role in fall prevention and in mitigating age-related functional decline.

Several limitations should be acknowledged when interpreting the findings of this study. The sample size was relatively small (n = 16), which, although comparable to similar mechanistic HDsEMG studies (Ely et al., 2022, Gamage et al., 2025), limits generalisability and may increase the risk of Type II error for smaller effects. The 4-week duration, while

sufficient to elicit neural adaptation, was relatively short to assess longer-term retention or structural change. Additionally, participants were healthy, high-functioning older adults, and the extent to which these results translate to frailer or clinical populations remains uncertain. Because this study did not include a non-exercise control group, placebo or expectancy effects cannot be completely excluded.

Although the improvements in MVC (≈ 10–15 %) and force steadiness (≈ 25 %) were statistically significant, these magnitudes are modest in absolute physiological terms and may not directly translate to large functional gains. However, such changes are consistent with those reported after short-term neural training interventions (Carroll et al., 2006a, Hendy and Lamon, 2017) and exceed typical day-to-day variability in force measurements (3–5 %; (Dideriksen et al., 2011)), suggesting that they represent genuine neural adaptations rather than measurement noise. Importantly, these neural-level improvements occurred without any heavy loading, highlighting the potential for FAT to improve neural precision even under low mechanical loads.

Taken together, while the present findings demonstrate that FAT can elicit measurable neural adaptations in the VL, these should be interpreted cautiously due to the small cohort size, short duration, and limited functional transfer data. Larger and longer studies are needed to confirm whether these neural improvements lead to meaningful changes in physical performance or fall risk in older populations.

Chapter 4: Effects of unilateral force accuracy training of the ankle dorsiflexors on bilateral neuromuscular function in older adults

4.1 Abstract

The tibialis anterior (TA) plays a critical role in gait, postural control, and balance, yet distal muscles remain underrepresented in neuromuscular training research. Age-related changes in motor-unit (MU) behaviour, including reduced discharge consistency and increased variability, compromise force steadiness and increase fall risk. Force Accuracy Training (FAT) provides a low-load, neural-targeted intervention that may enhance MU function in both trained and untrained limbs, but its effects on distal muscles such as the TA remain unclear.

Sixteen healthy older adults (73.8 ± 5.1 years; 8 female) completed four weeks of unilateral FAT of the TA (three sessions per week), followed by a four-week detraining period. Neuromuscular function was assessed pre-, post-, and at 2- and 4-weeks post-training. Primary outcomes included MU discharge rate (MUDR) and variability assessed via high-density surface electromyography (HDsEMG), alongside force steadiness (FS) and sinusoidal force-tracking accuracy (FTA). Secondary outcomes included maximal voluntary contraction (MVC) of the ankle dorsiflexors.

FAT elicited significant improvements in neuromuscular control. MVC increased by ≈ 10 % in the trained limb and ≈ 5 % in the untrained limb ($p < 0.05$), while FS improved by 20–25 % ($p < 0.01$) and FTA increased significantly ($p < 0.01$). These gains were largely maintained at 2 and 4 weeks of detraining. MUDR variability decreased by ~15 % ($p < 0.01$) in the trained TA, indicating enhanced temporal precision of MU firing, whereas MUDR itself showed a small but nonsignificant reduction, narrowing inter-limb differences. Compared with the vastus lateralis (VL) adaptations reported in Chapter 3, the

TA displayed smaller strength gains but greater improvements in force precision, underscoring muscle-specific neural adaptation.

Unilateral FAT enhances neuromuscular control of the TA in older adults, producing bilateral transfer and partial retention of benefits after detraining. The improvements in FS and tracking accuracy highlight FAT's potential to enhance gait stability and reduce fall risk, supporting its use as a practical, neural-focused intervention for maintaining lower-limb function in ageing populations.

4.2 Introduction

The tibialis anterior (TA) plays a critical role in functional mobility, contributing to ankle dorsiflexion, gait control, and postural stability (Perry and Burnfield, 2024). Weakness or impaired neuromuscular control of the TA is a known risk factor for gait abnormalities, reduced walking speed, and increased incidence of falls in older adults (Daubney and Culham, 1999). Despite its functional significance, the TA is often underrepresented in exercise interventions, which more commonly target larger proximal muscle groups such as the quadriceps (Piasecki et al., 2016d).

The decision to dedicate a separate chapter to the TA is grounded not only in its functional importance but also in its distinct neuromuscular architecture and age-related adaptation profile compared to proximal muscles, such as the vastus lateralis (VL). The TA contains a higher proportion of fatigue-resistant type I fibres (Johnson et al., 1973) and displays unique motoneuron properties. Recent evidence indicates that both persistent inward currents (PICs) and peak discharge rates (DRs) vary significantly across lower-limb muscles in young adults, with the TA showing greater PIC magnitude and higher peak DRs than the VL (Goreau et al., 2024, Kim et al., 2020). These muscle-specific properties

suggest divergent mechanisms of neural excitability and motor control, which may translate into muscle-specific responses to neuromuscular training.

Furthermore, the TA is engaged frequently in everyday locomotor tasks, including ankle dorsiflexion during the swing phase and postural corrections (Mortezanejad et al., 2024), potentially making it more resilient to age-related decline but also more dependent on precise neural modulation for effective control. Such physiological contrasts support the need to evaluate FAT effects in distal versus proximal muscles separately, particularly in older adults, where motor system plasticity is altered.

4.2.1 The role of FAT in enhancing the neuromuscular function

The TA is centrally involved in motor control of ankle dorsiflexion, which is critical for toe clearance during gait and for rapid postural adjustments following perturbations (Jacquelin Perry, 2010). Impairments in TA force control are associated with inefficient gait and increased risk of trips and falls (Daubney and Culham, 1999, Studenski et al., 2011). FAT targets neural pathways involved in precise force modulation, aiming to enhance FS, reduce variability in MU discharge, and improve overall neuromuscular function without the need for high load (Del Vecchio et al., 2019).

Although the TA experiences age-related neuromuscular changes such as motor unit (MU) remodelling and altered DRs (Power et al., 2013, Jones et al., 2022), it is generally better preserved than proximal muscles like the VL. It retains a higher number of functional MUs and more consistent force output, likely due to its frequent activation during everyday walking (Piasecki et al., 2016c, Piasecki et al., 2016d, Jones et al., 2021). In contrast, the VL experiences more marked MU loss and atrophy, often lacking sufficient compensatory reinnervation, particularly in individuals with sarcopenia (Piasecki et al., 2016d).

This differential vulnerability highlights the importance of comparing FAT-induced adaptations across muscles with distinct anatomical and physiological characteristics. Such analysis can reveal whether neural improvements are generalisable or muscle-specific, and whether distal muscles, despite being preserved, can still benefit from neural-targeted interventions like FAT.

4.2.2 Cross-education effects in distal muscles

The phenomenon of cross-education (CE), neuromuscular adaptations in the untrained contralateral limb, has been extensively documented in proximal muscle groups, but less so in distal muscles, such as the TA (Lee and Carroll, 2007b, Farthing, 2009). Nevertheless, the TA, due to its significant cortical representation and role in precise movement, may still exhibit meaningful CE effects following unilateral FAT. A different study has shown that strength and skill can transfer between limbs in both the upper and lower extremities, emphasising the adaptability of the neural pathways related to motor control (Green and Gabriel, 2018a). These effects are likely mediated through increased corticospinal excitability, interhemispheric facilitation, and reorganisation of cortical motor networks, providing functional benefits in untrained limbs even in the absence of direct exercise (Hendy and Lamon, 2017). Given the high degree of supraspinal control in TA function, the presence and extent of CE in this muscle may serve as a sensitive indicator of central plasticity in response to FAT.

4.2.3 Retention of FAT-induced adaptations

Assessing the retention of neuromuscular benefits following FAT is crucial for developing sustainable exercise strategies for older adults, especially those unable to engage in high-load resistance training. Evidence suggests that neural adaptations, such as enhanced MU recruitment and reduced discharge variability, can persist during detraining (Baxter et al.,

2024). Classic studies also showed that strength gains in older adults decline more slowly than muscle mass during detraining, consistent with lasting neural contributions (Taaffe and Marcus, 1997).

However, the extent to which these effects are maintained in distal muscles, such as the TA, remains unclear. While the TA may resist age-related decline due to frequent activation, it might also experience rapid functional loss if neural drive diminishes, making it essential to understand its detraining trajectory.

4.2.4 Study aims

This chapter evaluates the effects of a 4-week unilateral FAT intervention targeting the TA in healthy older adults aged 65 to 85 years. The primary aim is to determine the impact of FAT on strength and neuromuscular control, specifically FS, FTA, and MU behaviour assessed via HDsEMG. A secondary aim is to explore the presence of CE effects in the untrained limb and the extent to which these adaptations are retained during a 4-week detraining period. An additional objective is to assess whether the TA, as a relatively preserved distal muscle, demonstrates a distinct pattern of adaptation compared to the more age-affected VL when subjected to the same FAT protocol.

It was hypothesised that FAT would significantly improve neuromuscular function and force control in the trained TA, with secondary enhancements observed in the untrained limb via CE. It was further anticipated that these gains would persist at least partially following detraining, thereby supporting the long-term application of FAT as a practical and accessible strategy for preserving mobility and reducing fall risk in the ageing population.

4.3 Methods

4.3.1 Study overview

The methods used in this chapter mirror those described in Chapter 3.2 (VL-focused intervention), which investigated the effects of unilateral FAT on the knee extensors with a focus on VL. In that protocol, participants performed low-intensity isometric contractions of the right VL while the contralateral leg served as a within-subject control. The primary outcomes included force accuracy, muscle strength, balance, and functional mobility, with neuromuscular behaviour assessed using HDsEMG.

The primary outcomes in this chapter include TA MU discharge characteristics (MUDR and variability), FS, and FTA. Secondary outcomes include ankle dorsiflexor (ADF) MVC. The same group of healthy older adults (aged 65–85 years) participated in this phase of the study. All inclusion and exclusion criteria, recruitment procedures, and ethical approvals were identical to those described in Chapter 3.2.

In this chapter, the focus shifts to the TA, a key ankle dorsiflexor, to assess the effects of the same unilateral FAT protocol on distal neuromuscular function. Participants completed isometric FAT using their right leg's TA, with the left leg serving as the control limb. All testing and training procedures were conducted concurrently with the VL assessments, but the outcome measures and electrode placements were specific to the TA.

To target the TA, electrodes were positioned over the mid-belly of the muscle, approximately one-third of the way down from the tibial tuberosity to the lateral malleolus and aligned with the fibre direction (Figure 4.1). To assess the MVC of the ADF, participants were seated with their knee positioned at 90° flexion and the foot placed on a custom-built isometric dynamometer. The foot rested on a force-sensing plate, with a strap securing the forefoot to ensure stable contact while maintaining the heel on the plate.

Participants were instructed to dorsiflex their foot, pressing the ball of the foot upward against the strap, while keeping the heel grounded to isolate TA activation. FS and FTA were performed at 25% of the same-day MVC.

This study provides a unique comparison of neuromuscular adaptations in a relatively well-preserved distal muscle (TA) versus a more age-affected proximal muscle (VL), using the same intervention and timeline.



Figure 4.1 A custom-built dynamometer for the ankle and a high-density electromyography electrode placement over the tibialis anterior.

4.4 Results

4.4.1 Participant characteristics

All participants (n = 16; 8 females) completed the entire protocol, which included training and detraining assessments. Table 4.1 provides a summary of the baseline demographic and physiological characteristics.

Table 4.1 Participants characteristics (n = 16; 8 female)

Age (years)	73.8 (5.1)
Height (cm)	166.7 (6.8)
Weight (kg)	73.9 (10.4)
BMI (kg/m2)	26.6 (2.7)

Data shown as mean (standard deviation). *Abbreviations*: *BMI, body mass index.*

4.4.2 Functional measures

4.4.2.1 Ankle dorsiflexors MVC

For ADF MVC, a linear mixed-effects model revealed a significant quadratic effect of time ($p = .003$), indicating an increase followed by a decline over time (Figure 4.2A). There was no significant main effect of Leg ($p = .681$) and no Time × Leg interaction ($p = 0.587$). EMMs confirmed this pattern, with both legs increasing from Pre to Post ($p = 0.015$), and declining from Post2W to Post4W ($p = 0.032$). There was no significant difference between Pre and Post2w, or Post4W (both $p > 0.1$). These results suggest bilateral gains in strength post-training, with partial regression over the detraining period.

Table 4.2 Ankle dorsiflexors maximum voluntary contraction (MVC)

Group	Time	Mean (N)	SD	95% CI	Change vs. Pre
Control	Pre	155	40	[133, 177]	—
	Post	178	45	[154, 202]	+15% ↑ ($p = 0.015$)
	Post2W	175	42	[153, 197]	+13% (ns)
	Post4W	168	44	[145, 192]	+8% (ns) ↓ from Post ($p = 0.032$)
Exercise	Pre	157	38	[137, 177]	—
	Post	182	41	[160, 204]	+16% ↑ ($p = 0.015$)
	Post2W	178	40	[157, 199]	+13% (ns)
	Post4W	170	43	[147, 193]	+8% ↓ from Post ($p = 0.032$)

Abbreviations: N*, Newtons; SD, standard deviation; CI, confidence intervals.*

4.4.2.2 Force steadiness and sinewave tracking

For FS, a mixed-effects model revealed a significant Time × Leg interaction ($p = 0.013$), accompanied by a significant quadratic effect of time ($p = 0.024$) (Figure 4.2B). There was no significant effect of leg ($p=0.382$). EMMs revealed that FS declined (improved FS)

significantly over time in the trained leg, with significant reductions from Pre to Post ($p < 0.001$), Post2W ($p < 0.001$), and Post4W ($p < .001$). The FS in the control leg also decreased from Pre to Post ($p = 0.030$).

For sinewave tracking, a linear mixed-effects model revealed a significant linear increase ($p = 0.010$) and a significant quadratic effect ($p = 0.028$) in the CC of ADF during the sinewave task (Figure 4.2C). There was no significant effect of leg ($p=0.118$), but there was a significant leg x time linear interaction (both $p =0.042$). EMMs indicated this interaction was explained by a greater progressive increase in the trained leg only, which was significantly greater from Pre to Post, Pre to Post2W, and Pre to Post4W (all $p<0.002$). In the control leg, CC increased from Pre to Post only ($p=0.043$).

These findings suggest stronger, longer-lasting neural adaptations in the trained TA, with evidence of bilateral improvement in force precision.

Table 4.3 Ankle dorsiflexors Force steadiness (FS)

Group	Time	Mean (CoV)	SD	95% CI	Change vs. Pre
Control	Pre	0.085	0.022	[0.0733, 0.0967]	—
	Post	0.076	0.020	[0.0653, 0.0867]	−10 ↓ ($p = 0.030$)
	Post2W	0.074	0.021	[0.0638, 0.0842]	−12 ↓ (ns)
	Post4W	0.073	0.020	[0.0626, 0.0834]	−14 ↓ (ns)
Exercise	Pre	0.086	0.023	[0.0737, 0.0983]	—
	Post	0.067	0.021	[0.0568, 0.0772]	−22 ↓ ($p < 0.001$)
	Post2W	0.064	0.020	[0.0533, 0.0747]	−26 ↓ ($p < 0.001$)
	Post4W	0.063	0.021	[0.0528, 0.0732]	−27 ↓ ($p < 0.001$)

Abbreviations: CoV*, coefficient of variation; SD, standard deviation; CI, confidence intervals.*

Table 4.4 Ankle dorsiflexors force tracking accuracy (FTA)

Group	Time	Mean (CC)	SD	95% CI	Change vs. Pre
Control	Pre	0.88	0.05	[0.86, 0.90]	—
	Post	0.91	0.04	[0.89, 0.93]	+3% ↑ ($p = 0.043$)
	Post2W	0.92	0.04	[0.90, 0.94]	+4% (ns)
	Post4W	0.92	0.04	[0.90, 0.94]	+4% (ns)
Exercise	Pre	0.88	0.05	[0.86, 0.90]	—
	Post	0.93	0.04	[0.91, 0.95]	+6% ↑ ($p < 0.002$)
	Post2W	0.94	0.04	[0.92, 0.96]	+7% ↑ ($p < 0.002$)
	Post4W	0.94	0.04	[0.92, 0.96]	+7% ↑ ($p < 0.002$)

Abbreviations: CC, *Correlation Coefficient; SD, standard deviation; CI, confidence intervals.*

4.4.3 Electromyography (EMG)

For TA MUDR (Figure 4.3A), a linear mixed-effects model revealed a significant linear interaction ($p = 0.001$), a significant effect of leg ($p < 0.001$), but no significant effect of time (both $p > 0.35$). EMMs indicated no statistically significant decrease in either leg over time (all $p > 0.4$). However, there was a statistically significant difference across legs at Pre ($p < 0.001$) and Post ($p = 0.002$), with no difference at Post2W or Post4W (both $p > 0.2$). This suggests the interaction is explained by a decrease over time in the trained leg, resulting in a MUDR more similar to the control leg.

For TA MUDR variability (Figure 4.3B), there was no significant interaction (both $p > 0.78$), but there was a significant effect of leg ($p<0.001$) and a significant quadratic effect of time ($p=0.022$). EMMs indicated a higher variability in the control limb when compared to the exercise ($p<0.001$). DR variability was significantly reduced from Pre to Post ($p=0.005$) and from Pre to Post2W ($p=0.005$), with no further pairwise differences (all $p>0.3$).

Table 4.5 Tibialis anterior (TA) motor unit discharge rate (MUDR)

Group	Time	Mean (pps)	SD	95% CI	Change vs. Pre
Control	Pre	0.30	0.07	[0.263, 0.337]	—
	Post	0.31	0.07	[0.273, 0.347]	+3 % (ns)
	Post2W	0.30	0.07	[0.263, 0.337]	0 % (ns)
	Post4W	0.30	0.07	[0.263, 0.337]	0 % (ns)
Exercise	Pre	0.45	0.08	[0.407, 0.493]	—
	Post	0.38	0.08	[0.337, 0.423]	−16 % ↓ (p = 0.002)
	Post2W	0.34	0.07	[0.303, 0.377]	−24 % ↓ (ns)
	Post4W	0.32	0.07	[0.283, 0.357]	−29 % ↓ (ns)

Abbreviations: pps*, pulses per second; SD, standard deviation; CI, confidence intervals.*

Table 4.6 Tibialis anterior (TA) motor unit discharge rate (MUDR) variability

Group	Time	Mean (CoV)	SD	95% CI	Change vs. Pre
Control	Pre	0.36	0.07	[0.323, 0.397]	—
	Post	0.32	0.06	[0.288, 0.352]	−11% ↓ (p = 0.005)
	Post2W	0.31	0.06	[0.278, 0.342]	−14% ↓ (p = 0.005)
	Post4W	0.35	0.07	[0.312, 0.388]	+3% (ns)
Exercise	Pre	0.30	0.06	[0.268, 0.332]	—
	Post	0.26	0.06	[0.228, 0.292]	−13% ↓ (p = 0.005)
	Post2W	0.27	0.06	[0.238, 0.302]	−10% ↓ (p = 0.005)
	Post4W	0.30	0.06	[0.268, 0.332]	0% (ns)

Abbreviations: CoV*, coefficient of variation; SD, standard deviation; CI, confidence intervals.*

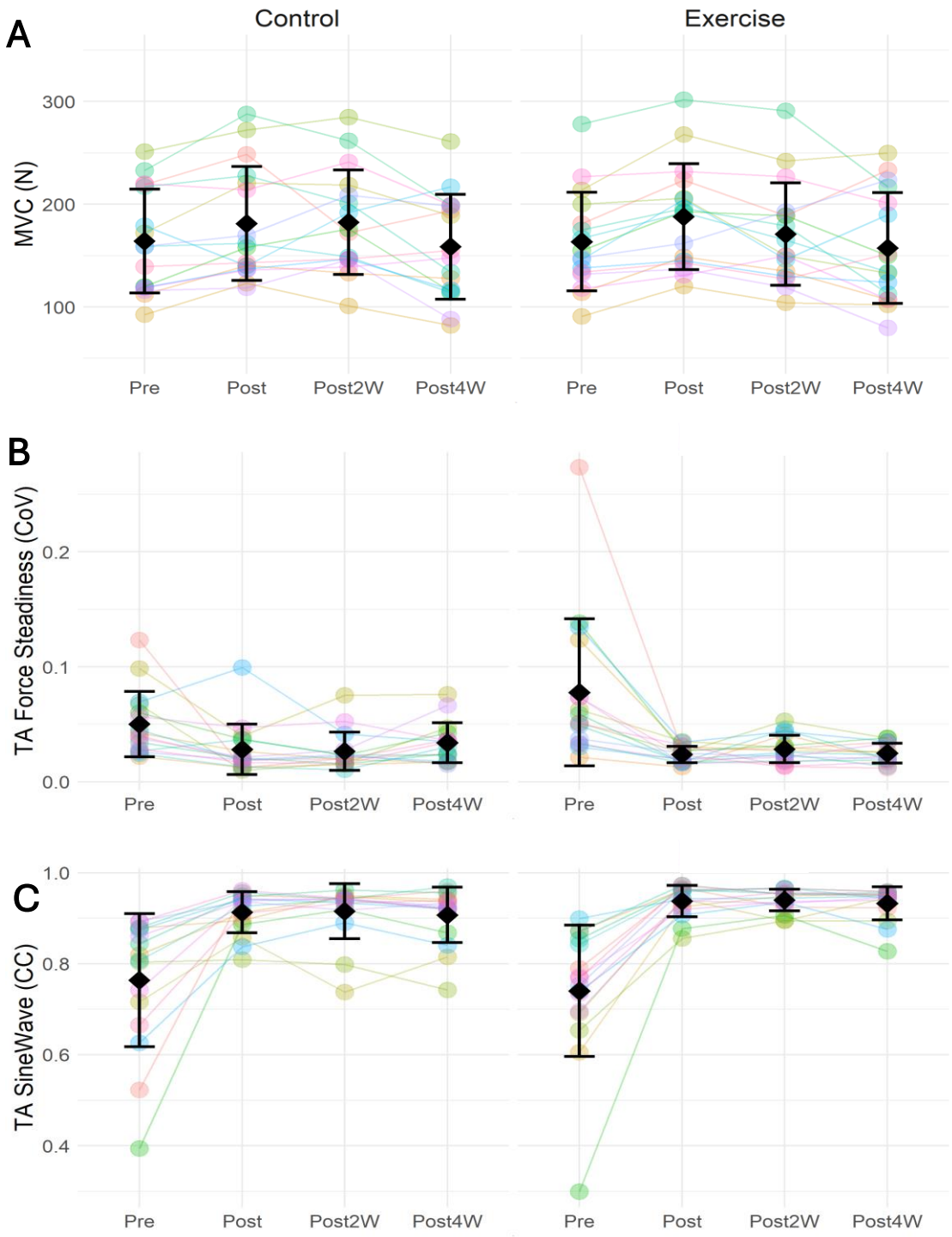


Figure 4.2 (A). Ankle dorsiflexor MVC; (B). Force steadiness and (C). Sinewave task of control and exercise limbs at Pre, Post, Post 2-weeks and Post 4-weeks intervention. MVC, maximum voluntary contraction; N, Newtons; TA, Tibialis Anterior; CoV, coefficient of variation; CC, Correlation Coefficient. Control and exercise groups are displayed separately where applicable. Black diamonds represent group means, black error bars indicate standard deviations (SD), and coloured circles show individual participant values, with lines connecting data from the same participant across time points.

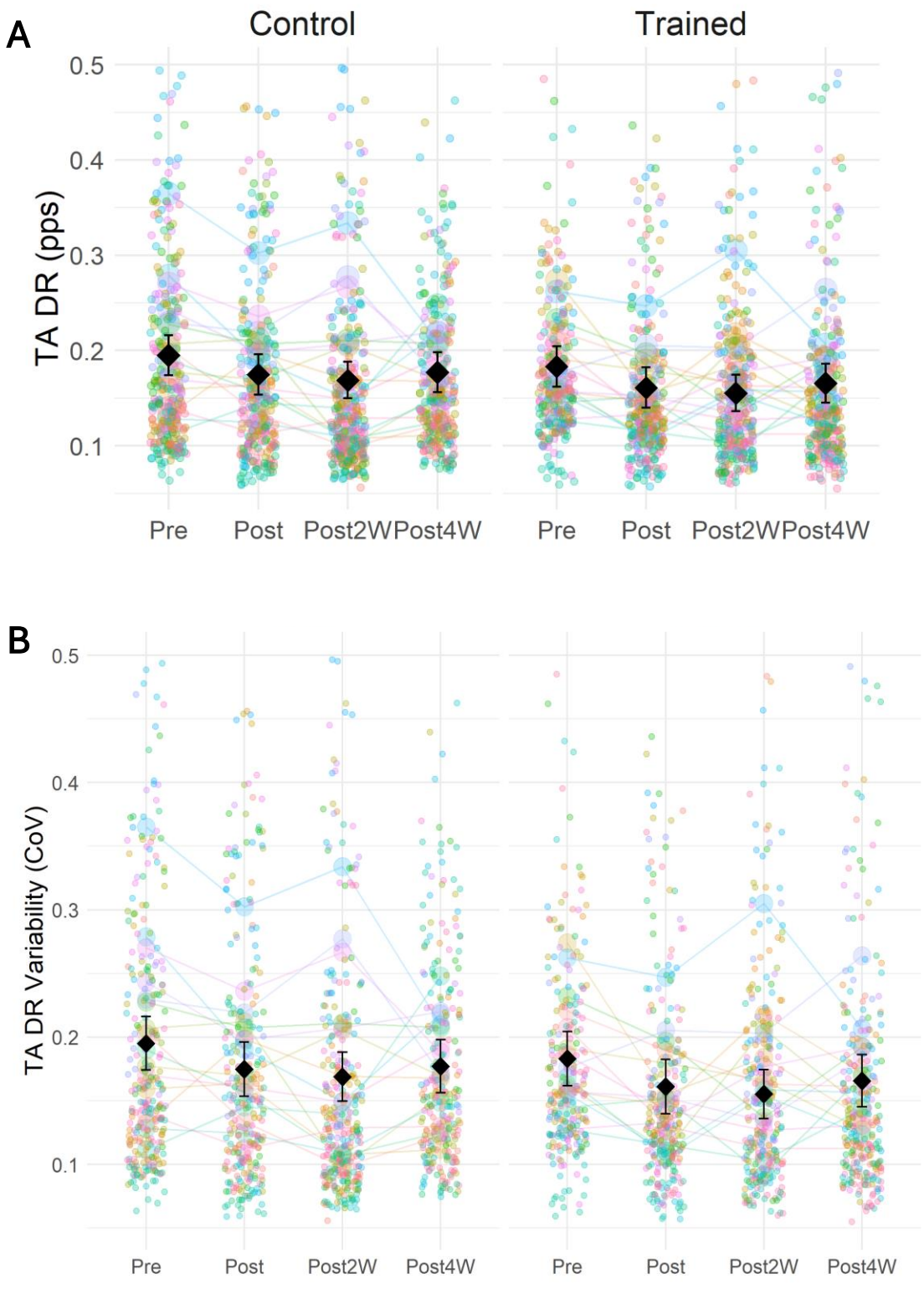


Figure 4.3 (A). TA discharge rate; and (B). TA discharge rate variability of control and exercise muscle at Pre, Post, Post 2-weeks and Post 4-weeks intervention. TA, Tibialis

Anterior; DR, discharge rate; pps, pulse per second; CoV, coefficient of variation. Control and exercise groups are displayed separately where applicable. Black diamonds and error bars represent estimated marginal means and 95% CI from model outputs. Large, coloured circles show individual participant means, with lines connecting data from the same participant across time points, and small coloured circles show individual motor unit values, colour-coded to participant.

4.5 Discussion

This chapter evaluated the effects of a 4-week unilateral low-intensity FAT protocol targeting the TA, a distal lower limb muscle that is relatively well-preserved with age. The primary findings revealed bilateral improvements in neuromuscular function, particularly in MVC, FS and FTA. The FS and FTA gains were largely retained at two- and four-week post-intervention, suggesting that FAT induces robust and durable neural adaptations. In contrast to the VL in Chapter 3, the TA showed more subtle but distinct changes in MU discharge characteristics. These differences likely reflect the distinct neurophysiological properties and age-related trajectories of proximal versus distal muscles.

Both limbs showed initial increases in dorsiflexor MVC post-intervention, with partial regression during detraining. While the lack of leg × time interaction suggests similar behaviour across limbs, it supports the presence of CE effects in strength gains. These results mirror findings from VL training (Chapter 3) and support earlier reports that neural adaptations can occur bilaterally even in the absence of mechanical loading (Orssatto et al., 2023, Del Vecchio et al., 2019).

Notably, the TA demonstrated a slightly faster regression in MVC by week 4 post-intervention compared to the VL. This may reflect either its lower absolute loading threshold or its greater reliance on habitual activation for strength maintenance. To our knowledge, no human studies have directly compared detraining responses between distal muscles such as the TA and proximal muscles like the VL. Animal research demonstrates

that fast muscles (e.g., plantaris) lose training adaptations more rapidly than highly active postural muscles (e.g., soleus), suggesting the plausibility of muscle-specific detraining timelines in humans (Hyatt et al., 2019).

FAT significantly improved FS and FTA in the trained ADF, with bilateral effects also observed. The significant decline in force variability and the increase in sinewave tracking accuracy suggest enhanced neuromuscular precision and motor output consistency. These results align with prior evidence that low-load, precision-based practice can reduce motor output variability in older adults via adaptations in central drive and sensory–motor integration (Christou, 2011, Taylor et al., 2003, Onushko et al., 2013, Kornatz et al., 2005). Improvements in FS are clinically meaningful given their association with better gait stability and lower fall risk in ageing populations (Enoka and Farina, 2021). Similarly, higher ankle dorsiflexion force variability has been linked to balance impairments and increased fall risk (Ko et al., 2025), reinforcing the functional importance of these findings. Interestingly, the control limb also demonstrated improvements in FS and FTA, although to a lesser extent. This provides further evidence of CE mechanisms extending beyond strength to motor precision, consistent with task-specific neural transfer effects (Green and Gabriel, 2018a). Given the TA's large cortical representation and role in finer motor control, these findings are physiologically plausible (Hendy and Lamon, 2017).

The EMG results revealed a subtle adaptation profile. While MUDR did not show significant changes over time, variability in discharge decreased significantly in the trained TA, indicating enhanced neural stability and motor control. The maintained or reduced variability is consistent with increased neural stability and improved motor control (Tracy et al., 2005a, Del Vecchio et al., 2019). This is particularly relevant in the TA, where MUDR variability is highly sensitive to neuromuscular interventions, such as

neuromuscular electrical stimulation (NMES) and voluntary isometric training (Borzuola et al., 2023). These findings suggest that the TA may be a promising target for interventions aimed at enhancing neuromuscular control in ageing and clinical populations. Additionally, at high contraction levels, the TA shows the highest MUDR of all lower-limb muscles, reflecting a unique neural drive profile (Inglis et al., 2025).

Interestingly, MUDR itself showed a trend toward decline in the trained leg, narrowing the baseline difference between limbs. Although it may seem counterintuitive, this could indicate improvements in neuromuscular efficiency, meaning enhanced performance with lower discharge rates (Enoka and Duchateau, 2017). Alternatively, it may reflect a compensatory redistribution of MU activity across the recruitment spectrum (Kamen and Knight, 2004) or, more speculatively, early signs of detraining, as suggested by previous longitudinal studies in older adults (Baxter et al., 2024, Taaffe and Marcus, 1997).

These findings emphasise the importance of interpreting MUDR alongside variability and functional outcomes. Unlike VL, where MUDR often increases or stabilises after training (Kamen and Knight, 2004, Vila-Chã and Falla, 2016), the TA may emphasise discharge consistency at low forces, while still attaining high DRs at high forces, reflecting a distinct neural control profile (Inglis et al., 2025). Moreover, cortical involvement in TA control is supported by EEG-EMG coherence and TMS work during locomotor tasks (Roeder et al., 2020, Gennaro and de Bruin, 2020).

The evidence of bilateral improvements in MVC, FS, and FTA, together with the narrowing of inter-limb differences in MUDR, supports centrally mediated CE (Calvert and Carson, 2022, Lee and Carroll, 2007b).

In distal ankle dorsiflexors such as TA, strong supraspinal involvement is evident from corticomuscular coherence and TMS studies during locomotor/postural tasks, suggesting

that central adaptations could facilitate contralateral benefits (Roeder et al., 2020, Petersen et al., 2012). Compared with VL, TA may exhibit a distinct control profile, with pronounced corticospinal engagement and task-dependent precision, while VL often shows increased stable discharge behaviour after training (Kamen and Knight, 2004, Eisner-Janowicz et al., 2023, Vila-Chã and Falla, 2016). These points justify analysing TA and VL responses separately in this thesis.

Enhancing TA precision has direct implications for gait safety and toe clearance, key fall-risk factors, given the TA's role in swing-phase dorsiflexion and its influence on minimum toe clearance (Perry and Burnfield, 2024, Daubney and Culham, 1999, Perera et al., 2021, Gambelli et al., 2023). Moreover, the ability to retain neuromuscular improvements beyond the cessation of training offers promise for clinical and community applications where adherence may be limited (Baxter et al., 2024, Kay et al., 2020).

This study also has limitations that should be considered. The sample size and training duration were identical to the VL study, and while this consistency aids comparability, the small cohort (n = 16) restricts statistical power to detect smaller effects. The absence of a control group and reliance on short-term follow-up prevent firm conclusions about long-term retention or causal mechanisms. Furthermore, participants were functionally independent older adults, and findings may not generalise to those with mobility limitations or clinical conditions.

The statistically significant improvements in FS (~20–25 %) and FTA (~15–20 %) represent small-to-moderate physiological changes in absolute terms, but these are meaningful when considered in the context of age-related declines in force control (Christou and Enoka, 2011a, Hunter et al., 2016). Force steadiness is strongly linked to balance performance and fall risk (Liu et al., 2014, Lord et al., 2003); therefore, even

modest neural improvements could have practical value in maintaining stability during daily activities. However, the observed increases in MVC (≈ 10 %) are unlikely to translate into clinically significant strength improvements.

In summary, the TA exhibited smaller strength gains but greater precision improvements compared with the VL, suggesting muscle-specific neural responsiveness. These findings should nonetheless be viewed as preliminary and physiologically modest until confirmed by studies with larger, more diverse cohorts and direct functional outcome measures.

Future studies should explore longer training durations, task-specific carryover to gait metrics, and neuroimaging correlates of CE. Additionally, comparisons between concentric, eccentric, and isometric FAT in the TA may elucidate optimal protocols for targeting MU plasticity in distal muscles.

Chapter 5: Bilateral neuromuscular asymmetry in stroke survivors

5.1 Abstract

Stroke is a leading cause of long-term disability, often resulting in profound neuromuscular impairments. While rehabilitation has traditionally focused on the paretic limb, emerging evidence indicates that neural deficits may also affect the non-paretic side. This study aimed to characterise bilateral neuromuscular function in stroke survivors compared with age-matched healthy older adults, focusing on motor-unit (MU) behaviour, force control, and strength.

Ten chronic stroke survivors (4 male, 6 female; mean age = 72 ± 6 years) and sixteen healthy older adults (8 female) completed assessments of the tibialis anterior (TA). Outcomes included maximal voluntary contraction (MVC), force steadiness (FS), sinusoidal force-tracking accuracy (FTA), and MU discharge characteristics obtained using high-density surface electromyography (HDsEMG). Comparisons were made between paretic, non-paretic, and control limbs.

Stroke survivors exhibited marked bilateral neuromuscular impairments. MVC was ~45 % lower in the paretic limb and ~20 % lower in the non-paretic limb compared with controls ($p < 0.001$). FS was impaired by approximately 25–30 % ($p < 0.01$) and FTA performance decreased significantly ($p < 0.01$) in both limbs relative to controls. HDsEMG revealed reduced motor-unit discharge rates (~15 % lower) and greater discharge variability ($p < 0.01$) in the paretic limb, while the non-paretic limb also showed elevated variability (~10–12 % higher than controls), confirming bilateral neural dysfunction.

These findings demonstrate that neuromuscular deficits after stroke extend beyond the paretic side, indicating widespread neural reorganisation that compromises motor control

bilaterally. Such impairments likely contribute to asymmetrical movement patterns and heightened fall risk. The results underscore the need for rehabilitation strategies that target both limbs, supporting the potential role of neural-focused interventions such as Force Accuracy Training (FAT) and cross-education (CE) to restore function and improve bilateral motor coordination.

5.2 Introduction

5.2.1 Stroke

Stroke is a major global health problem, characterised by the sudden onset of neurological deficits due to an acute interruption in the blood supply to the brain. This interruption can be caused by a blockage or bleeding, causing ischemic stroke or haemorrhagic stroke, respectively (Johnson et al., 2016). Globally, stroke is recognised as the second leading cause of death and a major contributor to long-term disability, accounting for approximately 11% of all deaths worldwide (Feigin et al., 2022). To exemplify this burden numerically, worldwide, approximately 12.2 million people suffer a new stroke each year, with around 6.5 million deaths attributed to stroke annually (GBD, 2019, Feigin et al., 2021). Despite advances in acute care and secondary prevention, both the prevalence (Figure 5.1A) and mortality (Figure 5.1B) of stroke continue to rise in many regions, particularly in low- and middle-income countries where healthcare resources are often limited (GBD, 2019, Liu et al., 2025).

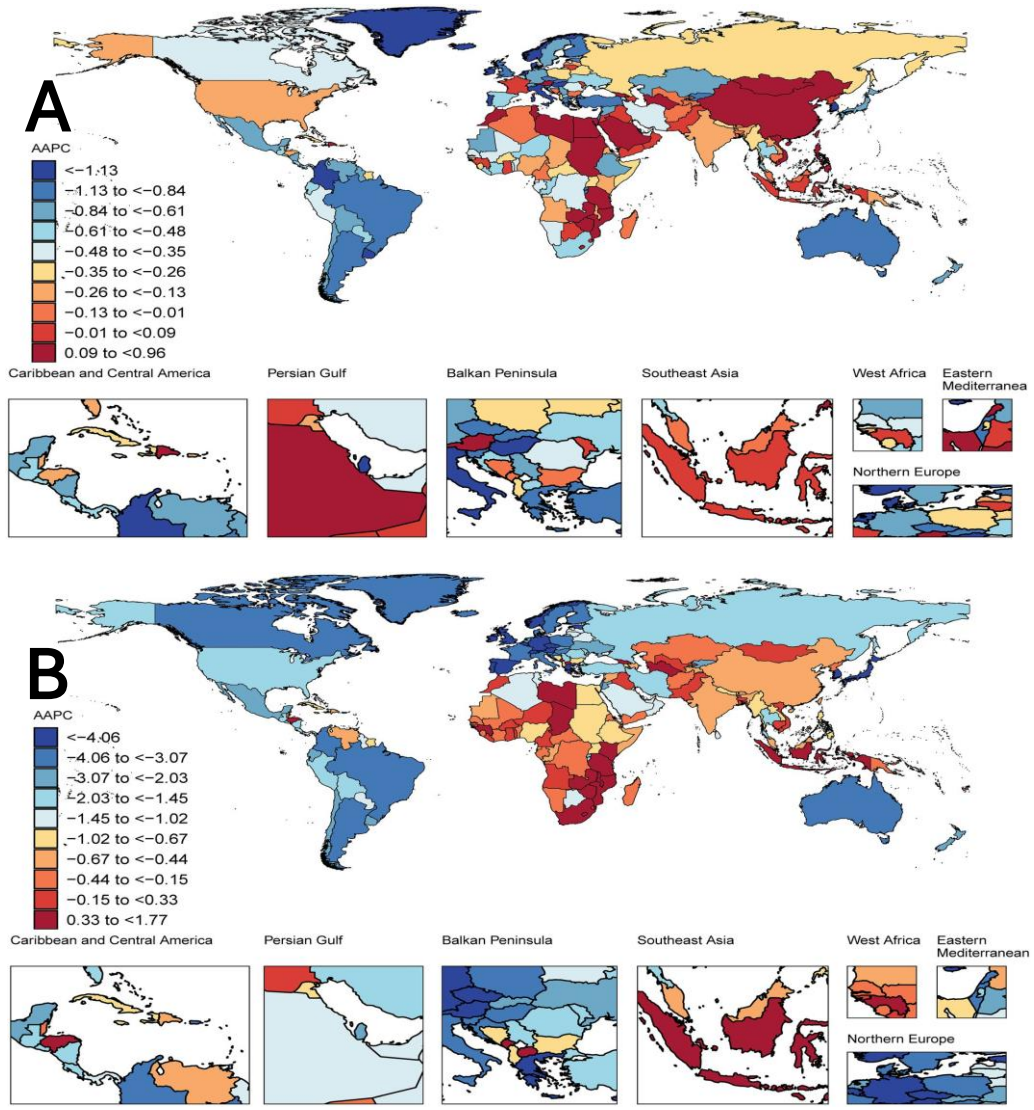


Figure 5.1 Global maps illustrating the average annual percentage change in (A) stroke prevalence and (B) stroke-related mortality among individuals aged 20 years and older from 1990 to 2021, adapted from (Liu et al., 2025).

Stroke pathophysiology is characterised by a complex interplay of vascular, cellular, and molecular processes. In ischemic stroke, cerebral artery occlusion triggers a cascade of events, including energy failure, excitotoxicity, oxidative stress, and inflammation, that ultimately lead to neuronal death (Deb et al., 2010). Haemorrhagic stroke, on the other hand, is characterised by the rupture of blood vessels, leading to increased intracranial pressure and secondary brain injury (Qureshi et al., 2009).

Risk factors for both types of strokes include non-modifiable elements (age, sex, genetics) and modifiable ones (hypertension, diabetes, dyslipidaemia, smoking, and physical inactivity), with hypertension being the most influential and preventable contributor to both stroke types. This is because chronically elevated blood pressure induces endothelial dysfunction, promotes atherosclerosis, and increases arterial stiffness, thereby raising the risk of thromboembolic events and vessel rupture (O'Donnell et al., 2010, Iadecola and Davisson, 2008) (Figure 5.2).

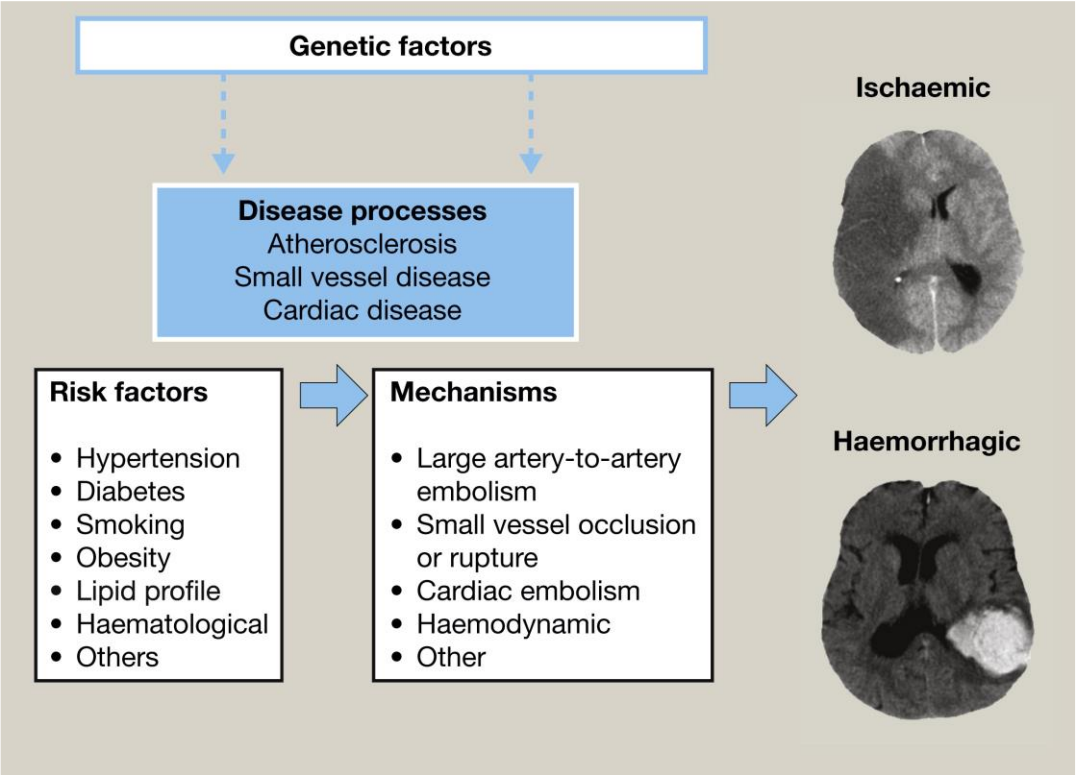


Figure 5.2 Illustration of differences between disease process, risk factors and mechanisms in strokes, adapted from (Murphy and Werring, 2020).

5.2.2 The public health burden of stroke

Stroke places a heavy burden on sufferers, families, and healthcare systems worldwide. Including medical costs, productivity losses, and informal care, the economic impact of

stroke is vast, with an estimated annual cost of £26 billion in the UK alone (Luengo-Fernandez et al., 2020).

Stroke incidence, outcomes, and access to care vary widely between populations and indeed regions. Factors such as socioeconomic status, education level, and availability of healthcare services play a critical role in determining stroke risk and recovery (Pandian et al., 2020). In wealthier countries, the incidence of stroke has declined in recent years thanks to better risk factor management and advances in acute care. By contrast, in low- and middle-income countries, where healthcare systems are often under-resourced, the burden of stroke continues to grow (Feigin et al., 2021). Illustrating this disparity, in the UK, the age-standardised stroke incidence is approximately 115 per 100,000 population per year, with declining mortality due to robust prevention and emergency care systems (PHE, 2018). In contrast, India reports an age-standardised incidence of 145 per 100,000, with significantly higher case fatality and disability-adjusted life years, reflecting limited access to acute stroke care and rehabilitation services (Pandian and Sudhan, 2013, Kalkonde et al., 2023).

Efforts to reduce the global burden of stroke primarily focus on prevention, early detection, and timely access to treatment. Public health strategies aimed at promoting lifestyle modifications, managing vascular risk factors, and improving healthcare access have shown meaningful reductions in stroke incidence and recurrence, particularly in high-income countries (Owolabi et al., 2022, Feigin et al., 2021). Specifically, interventions such as increasing physical activity, reducing dietary salt intake, smoking cessation, and weight management have consistently been identified as effective preventive measures (Owolabi et al., 2022, O'Donnell et al., 2016). These lifestyle changes, when implemented through

population-wide and high-risk strategies, have been linked to significant reductions in stroke and cardiovascular disease (Yusuf et al., 2020, He et al., 2020).

5.2.3 Stroke and neuromuscular function

Stroke can profoundly impact neuromuscular function, leading to a broad spectrum of motor, sensory, cognitive, and psychological deficits. The severity and type of impairment depend primarily on the location, size, and laterality of the lesion, as well as the brain structures and descending tracts involved. Common neuromuscular deficits following stroke include hemiparesis, spasticity, muscle weakness, disordered motor unit (MU) behaviour, and impaired balance and coordination (Langhorne et al., 2011, McPherson et al., 2018).

Hemiparesis, defined as weakness or abnormal muscle activation patterns on one side of the body, affects approximately 80% of stroke survivors and is a major contributor to long-term disability (Nakayama et al., 1994a). Further, spasticity, characterised by increased muscle tone and exaggerated tendon reflexes, is observed in about 30% of stroke patients and can further hinder mobility and functional independence (Sommerfeld et al., 2004).

These motor impairments typically occur contralateral to the lesion due to the decussation of corticospinal tracts in the medulla. Left-hemispheric strokes often result in right-sided motor impairments and are more commonly associated with aphasia and apraxia, while right-hemispheric strokes lead to left-sided weakness and are frequently linked with visuospatial neglect and attentional deficits (Hedna et al., 2013, Stone et al., 1993).

From a neuromuscular control perspective, these hemispheric differences can influence recovery patterns, coordination, and motor planning. For instance, damage to the right hemisphere may compromise spatial awareness and sensorimotor integration, while left-

hemisphere strokes may more severely affect fine motor control, planning, and sequential task execution (Corbetta and Shulman, 2011).

Recent evidence has highlighted substantial changes in neuromuscular control after stroke, including impaired MU recruitment strategies, reduced MU discharge rate (MUDR), and increased discharge variability (Li et al., 2014, Beauchamp et al., 2023). These impairments are not limited to the paretic side. Instead, studies suggest that the non-paretic limb may also exhibit reduced strength, altered MU behaviour, and diminished functional capacity compared to age-matched controls (Dragert and Zehr, 2013, Beauchamp et al., 2023). Such bilateral deficits likely reflect systemic neural changes, including interhemispheric inhibition and contralesional reorganisation of motor pathways.

In addition to motor impairments, stroke can also affect sensory and perceptual functions. Sensory deficits, such as loss of sensation, impaired proprioception, or altered perception, are prevalent and have been shown to impair movement coordination, reduce balance, and delay recovery of gait and upper limb function (Connell et al., 2008, Carey, 1995). These deficits are especially problematic as they often go under-recognised but can significantly interfere with motor relearning and rehabilitation outcomes.

Cognitive impairments, including difficulties with attention, working memory, and executive function, are also common and further complicate recovery. Cognitive deficits have been reported in up to 60% of stroke survivors in the subacute phase and are strongly associated with reduced engagement in rehabilitation and poorer long-term outcomes (Beyaert et al., 2015). Executive dysfunction can affect a patient's ability to sequence tasks, monitor performance, and maintain motivation during therapy.

The psychological consequences of stroke are also considerable, with survivors often experiencing depression, anxiety, and post-stroke fatigue. These psychosocial challenges

can impede recovery, diminish quality of life, and place additional strain on caregivers and healthcare systems (Hackett et al., 2005). Neuropsychiatric sequelae may also be influenced by the lesion location, with left-sided strokes more strongly linked to depression, while right-sided lesions may contribute to anosognosia and disengagement.

Despite these well-established clinical features, the neuromuscular mechanisms underpinning bilateral deficits post-stroke remain poorly characterised. Most prior work has focused on strength measures or clinical mobility tests, offering limited mechanistic insight into MU level changes driving these impairments. Very few studies have employed high-resolution neurophysiological techniques such as high-density surface electromyography (HDsEMG) to assess discharge rate (DR), variability, or recruitment patterns in both paretic and non-paretic limbs. For example, Li et al. (2014) applied HDsEMG to compare motor unit firing behaviour in paretic versus contralateral first dorsal interosseous muscles, revealing elevated discharge variability post-stroke (Li et al., 2014). Similarly, Kallenberg and Hermens (2009) used multichannel surface EMG to demonstrate that motor unit properties differ between paretic and non-paretic biceps, suggesting altered recruitment strategies (Kallenberg and Hermens, 2009). This scarcity of bilateral HDsEMG investigation contrasts sharply with the abundant mechanistic literature on healthy ageing, highlighting a significant gap in our understanding.

As outlined above, neuromuscular deficits after stroke extend beyond overt weakness or hemiparesis to involve complex alterations across cortical, subcortical, spinal, and muscular systems. These mechanisms remain neither fully understood nor consistently measured by objective neurophysiological tools. Therefore, the aim of this study was to characterise bilateral neuromuscular impairments in stroke survivors using detailed assessments, force steadiness (FS), sinusoidal tracking accuracy (FTA), MUDR, and

discharge variability, and, crucially, to compare these with healthy age-matched controls to distinguish deficits attributable to stroke from those due to healthy ageing.

5.2.4 Neuromuscular rehabilitation of stroke

According to the World Health Organisation (WHO) (2018, p. 5), rehabilitation is defined as "a set of interventions designed to optimise functioning and reduce disability in individuals with health conditions in interaction with their environment." It is a mainstay of stroke recovery pathways. Neuromuscular rehabilitation plays a pivotal role in this process, aiming to restore motor function, promote independence, and enhance overall quality of life (WHO, 2018).

Rehabilitation strategies are diverse and most often tailored to individual needs rather than based on set protocols. These strategies commonly incorporate physical therapy, occupational therapy, speech-language therapy, and, more recently, innovative techniques such as robotic-assisted therapy, virtual reality-based interventions and neuromuscular electrical stimulation.

The primary goal of neuromuscular rehabilitation is to promote neuroplasticity, the brain and central nervous system’s ability to reorganise and form new neural connections. Neuroplasticity is a key mechanism underlying functional recovery following stroke, allowing undamaged areas of the brain to compensate for lost function (Dimyan and Cohen, 2011). Rehabilitation strategies that enhance neuroplasticity, such as task-specific training and repetitive practice, have been found to be crucial for maximising recovery potential (Kleim and Jones, 2008).

Physical therapy is a cornerstone of stroke rehabilitation, focusing on improving strength, coordination, balance, and mobility. Techniques such as constraint-induced movement therapy (CIMT), treadmill training, and functional electrical stimulation (FES) have each

been shown to enhance motor recovery and functional outcomes (Langhorne et al., 2011, Mehrholz et al., 2017). Occupational therapy is equally important, emphasising the development of skills needed for activities of daily living (ADLs) and instrumental activities of daily living (IADLs). Occupational therapy interventions may include task-oriented training, adaptive techniques, and environmental modifications to enhance functional independence and quality of life (Cramer and Riley, 2008).

Innovative rehabilitation technologies, such as robotic-assisted therapy and virtual reality, offer promising avenues for enhancing recovery. Robotic devices can provide high-intensity, repetitive practice with precise feedback, facilitating motor learning and recovery (Kwakkel et al., 2008). Virtual reality systems can create immersive environments that encourage engagement and motivation, supporting functional improvements (Laver et al., 2015).

In addition to physical rehabilitation, addressing psychosocial issues is crucial for comprehensive stroke care. Psychological interventions, such as cognitive-behavioural therapy and motivational interviewing, can support emotional well-being and subsequently enhance rehabilitation outcomes (Hackett and Pickles, 2014).

The timing and intensity of rehabilitation are critical factors influencing recovery. Early initiation of rehabilitation is associated with better outcomes, as it capitalises on the brain's reinforced state of plasticity following injury (Tailor et al., 2017). For example, Langhorne et al. (2011) reported that patients who began rehabilitation within 24–48 hours of stroke onset demonstrated significantly better functional outcomes at 3 months compared to those who started after 7 days (Langhorne et al., 2011).

Intensive rehabilitation, characterised by high frequency and duration of therapy sessions, has been shown to improve functional outcomes and reduce disability. In a meta-analysis

by Lohse et al. (2014), increased therapy dosage was positively correlated with better motor outcomes. Specifically, interventions involving ≥3 hours per day of task-specific therapy over 5–6 days per week were associated with significantly greater improvements in upper limb function than lower-intensity protocols (Lohse et al., 2014).

To exemplify, patients receiving 60-minute sessions five times per week showed greater improvements in Fugl-Meyer motor scores and ADL performance than those receiving two 30-minute sessions per week (Kwakkel et al., 1999). These findings support the importance of both early and intensive intervention in optimising neuroplastic recovery trajectories post-stroke.

Despite advancements in stroke rehabilitation, challenges remain. Barriers to access, variability in rehabilitation services, and limited resources in low- and middle-income countries hinder the provision of effective rehabilitation for all. Addressing these challenges requires a concerted effort to improve healthcare infrastructure, enhance training for healthcare professionals, and promote research and innovation in rehabilitation strategies (Lindsay et al., 2019, Pandian and Sudhan, 2013), a great challenge for all countries, but especially so for those with limited resources.

5.2.5 Stroke versus ageing: a neuromuscular perspective

While ageing itself leads to MU loss, remodelling, and increased discharge variability (Piasecki et al., 2016b, Hepple and Rice, 2016), stroke introduces a distinct set of neural impairments that may exacerbate these changes, including disrupted corticospinal drive, disordered recruitment, impaired DR modulation, and abnormal synergies (Beauchamp et al., 2023, Dragert and Zehr, 2013, Li et al., 2014) or elicit a unique profile of impairment.

5.2.6 Aim and objectives

Based on the existing literature and the apparent knowledge gaps that remain, the primary aim of the study presented in this chapter was to characterise bilateral neuromuscular deficits in stroke survivors and to determine whether stroke-related impairments differ from those seen in healthy older adults.

The specific objectives were to quantify bilateral differences in muscle and neuromuscular function between the paretic and non-paretic limbs of stroke survivors, and to compare these measures with those of age-matched healthy older adults in order to assess the relative impact of stroke versus ageing.

It was hypothesised that stroke survivors would demonstrate impairments in both muscle and neuromuscular function, with these deficits being more pronounced in the paretic limb than in the non-paretic limb.

5.3 Methods

5.3.1 Ethical approval

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (WMA, 2013). Ethical approval was obtained from the University of Nottingham Faculty of Medicine and Health Sciences Research Ethics Committee (FMHS 188-0524), and the study was registered on www.ClinicalTrials.gov (NCT07013188). The full ethics application for this study can be seen in Appendix III.

5.3.2 Participants

The sample size for this observational comparison was estimated using data from previous studies reporting large differences in force steadiness (FS) between chronic stroke survivors and healthy older adults. Lodha et al. (2013) found that FS variability in the paretic limb was approximately 1.5–2 times greater than in controls, corresponding to a large

standardised effect size (d ≈ 1.2–1.5). Similar reports of increased variability and impaired MU firing behaviour in stroke further confirm large neuromuscular deficits (Bowden et al., 2014). Assuming a two-tailed test, α = 0.05 and power = 0.80, a large effect size of d = 1.3 would require about n ≈ 9 per group (Cohen, 2013, Faul et al., 2009). Accordingly, recruiting ten stroke participants and sixteen controls was considered sufficient to detect major between-group differences in FS and related outcomes.

Comparisons between limbs within the stroke group were exploratory, as no prior data exist quantifying bilateral limb differences in MU behaviour after stroke. These analyses, therefore, provide preliminary estimates to inform future power calculations.

5.3.2.1 Eligibility

Ten post-stroke survivors, comprising four males and six females, were recruited from the community using posters, social media advertisements, and direct outreach through the Derby Stroke Club. Thirteen individuals were screened, and three were excluded due to not meeting the inclusion criteria. Eligibility for participation was assessed against the following criteria:

Inclusion criteria

- Aged over 18 years old
- Willing and able to give informed consent for participation in the study
- Had a confirmed stroke within the last 5 years
- Self-report of a persisting post-stroke deficit in unilateral limb function

Exclusion criteria

- Diagnosis of cognitive impairment/dementia
- Current or recent (<2y) malignancy
- Severe respiratory disease*

- Active cardiovascular or renal disease*
- Severe metabolic disease*
- Significant musculoskeletal disorder*
- Recent (<6 months) steroid treatment or hormone replacement therapy
- Wheelchair dependency

**As determined by a clinician at screening*

This health profile was selected to ensure a relatively homogeneous population of post-stroke patients capable of safely completing neuromuscular assessments.

The healthy volunteers presented in this chapter are the same cohort outlined in Chapters 3 and 4, with the eligibility criteria for those individuals outlined in 3.2.2. Eligibility criteria for these individuals were largely the same as for our stroke patients, with the exception of past stroke and persisting post-stroke functional deficit. In addition, our healthy volunteers were required to be over the age of 65y. Whilst there was no minimum age requirement for our stroke patients, given the heightened prevalence of stroke with advancing age, and the average age of stroke in the UK being 70-73 years (Stroke_Association, 2023), we anticipated a stroke population with a comparable age to our healthy controls, facilitating our comparison of assessing the additional impact of stroke (beyond ageing) on neuromuscular function.

5.3.2.2 Study overview

This study employed an observational case-control design with a nested within-subject comparison between legs. All participants completed a single assessment session involving the same outcome measures previously described in Chapter 3.2. In brief, these assessments included measures of muscle and neuromuscular function.

Although a healthy control cohort was included for comparative purposes, the study was not a registered randomised controlled trial. The healthy group acted as a reference comparison rather than a prospectively registered control arm, since no intervention or randomisation was applied. The main objective was to compare bilateral neuromuscular characteristics of stroke survivors with age-matched healthy adults under identical assessment conditions. This approach aligns with the observational nature of the investigation while acknowledging that a formal case–control or longitudinal design could strengthen causal inference in future studies.

5.3.2.3 Screening visit

Prior to enrolment, all stroke participants attended a screening session to determine their eligibility for the study. This included an electrocardiogram (ECG), blood pressure measurement, and a comprehensive review of general health and medical history. Having had the Participant Information Sheet (PIS) for a minimum of 48-hours prior to this visit, participants had the opportunity to ask any questions regarding study procedures at this visit. In cases of abnormal screening results, findings were discussed with the participant, and their general practitioner (GP) was notified in writing.

Demographic data, including age, sex, height, weight, and body mass index (BMI), were recorded at this session. Informed written consent was obtained from all participants at this session before any procedures. Those who met the inclusion criteria were invited to complete a single assessment session within the ensuing 4-weeks.

5.3.2.4 Assessment visit

Following the screening, eligible participants attended a laboratory-based assessment session at ~0900h (±1 hour). This single visit, lasting approximately four hours, included a

detailed explanation of each testing component and provided ample time for rest between assessments.

The primary objective of these visits was to evaluate bilateral neuromuscular and muscle function in stroke survivors and compare these outcomes with data previously collected from healthy older adults (see Chapters 3 and 4). All outcome measures and protocols were consistent with those used in the earlier chapters, ensuring methodological comparability. The only exception to this was completion of the post-stroke questionnaires which were completed by the stroke patients only to further characterise this group. A schematic of the assessment day can be seen in (Figure 5.3).

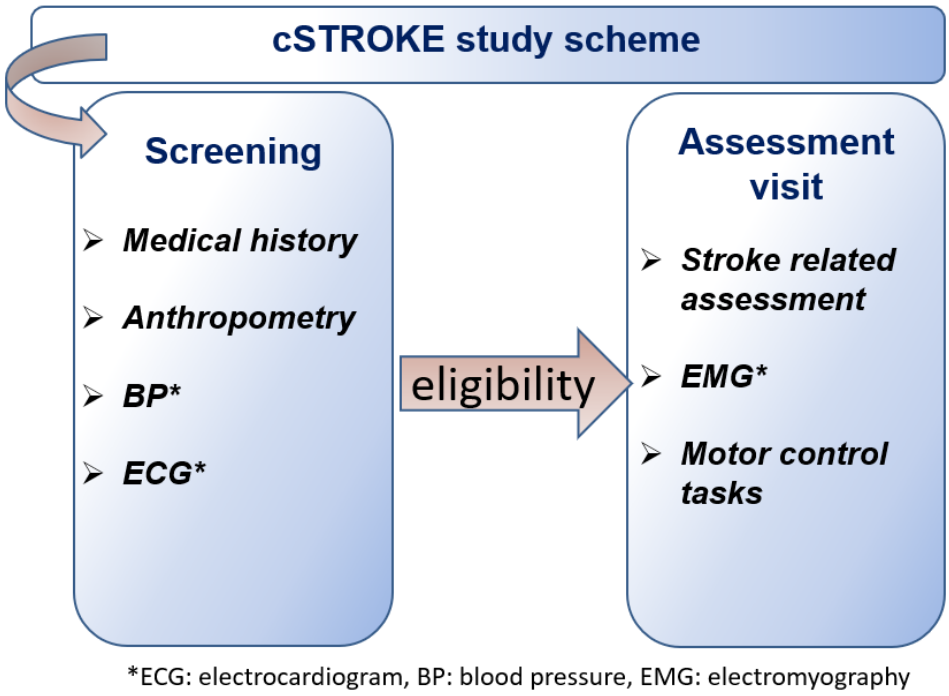


Figure 5.3 A schematic of the stroke study visits.

5.3.3 Measurable endpoints

5.3.3.1 Global disability

Global disability was assessed using the Modified Rankin Scale (mRS), a widely used measure of overall functional independence following stroke. The mRS measures disability through 7 ordinal scale points (0 = no symptoms, 6 = death) (van Swieten et al., 1988). The whole mRS can be seen in Appendix III.

5.3.3.2 Patient-reported stroke impact

The Stroke Impact Scale version 2 (SIS) is a self-reported measure that assesses eight domains of functioning: i) strength, ii) hand function, iii) mobility, iv) instrumental/activities of daily living (ADL/IADL), v) impairment in muscle function, vi) emotion, vi) memory and thinking, vii) communication, and viii) participation. Scores for each domain were standardised on a 0–100 scale, where higher scores indicate better perceived function (Duncan et al., 1999). The full SIS can be seen in Appendix III.

5.3.3.3 Fugl-Meyer assessment

The Fugl-Meyer Assessment (FMA), a motor impairment assessment subscale, is a validated tool designed to evaluate motor function in individuals recovering from stroke (Fugl-Meyer et al., 1975). It encompasses four primary domains: i) reflex activity, ii) volitional movement within synergy, iii) volitional movement outside of synergy, and iv) coordination and speed. Each item is scored on a 3-point ordinal scale whereby 0 = cannot perform, 1 = performs partially, 2 = performs fully. The maximum score is 66 for the upper limb (FMA-UE) and 34 for the lower limb (FMA-LE), with higher scores indicating better motor function. The full FMA can be seen in Appendix III.

5.3.3.4 Isometric strength

MVC of the ankle dorsiflexors (ADF) were measured using isometric dynamometry on a custom-built dynamometer (same as chapter 4.3.1). Unilateral handgrip strength was

assessed via a handgrip dynamometer (T.K.K. A5401, Takei Scientific Instruments, Niigata, Japan). For a full description of these methods, see chapter 3.2.4.

5.3.3.5 Motor control

Participants performed low-intensity isometric force-tracking tasks using their ADF. A real-time visual trace was displayed on a screen, with the task scaled to the individual's MVC. Two tasks were used to assess neuromuscular control. In the FS task (Figure 5.4A), Participants were instructed to maintain a constant submaximal force output (typically 25% MVC) by matching a trapezoid-shaped target as steadily as possible. This task evaluates the ability to sustain a stable motor unit output over time. Performance was quantified using the coefficient of variation (CoV), which represents the relative variability of the force signal around the target. Lower CoV values indicate steadier force and better control, whereas higher values indicate greater fluctuations and poorer steadiness.

In the sinusoidal FTA (Figure 5.4B), participants were instructed to follow a moving sinusoidal waveform by rhythmically modulating their force output. This task assesses dynamic motor coordination, requiring smooth, well-timed increases and decreases in force. Performance was quantified using:

- Correlation coefficient (CC): Indicates how closely the shape of the participant’s force trace matches the target waveform. Values closer to 1.0 reflect greater similarity in timing and pattern of force fluctuations.
- Area under the curve (AUC): Quantifies the total deviation between the produced force and the target waveform over the entire tracking period, with higher values representing greater overall tracking error, regardless of whether the error follows the correct pattern.

For a full description of these methods, see Section 3.2.4.5.

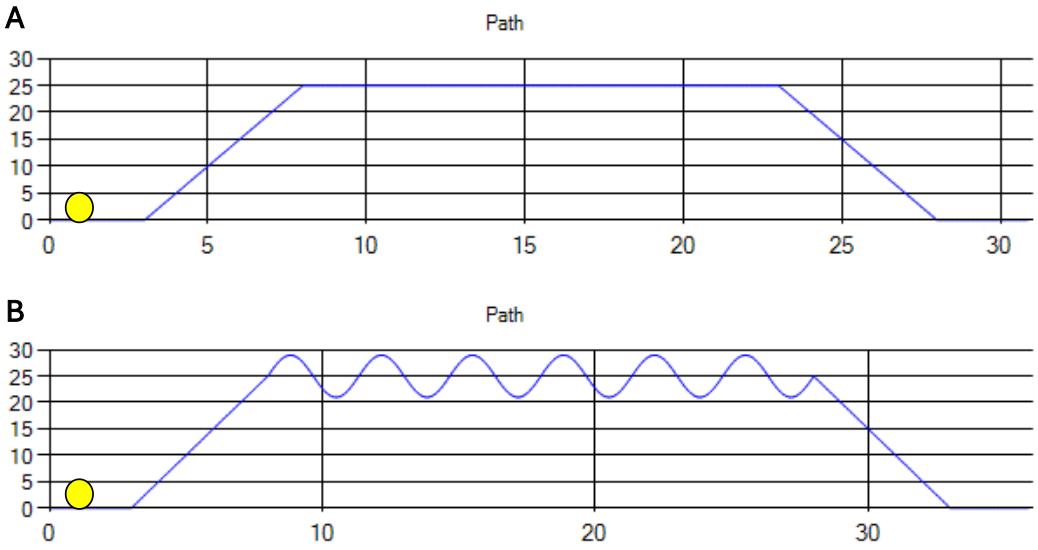


Figure 5.4 An example for (A). force steadiness task setup and (B) sinusoidal force tracking accuracy task setup. Participants were asked to follow the blue line by rhythmically modulating their force output.

5.3.3.6 High-density surface electromyography (HDsEMG)

Bilateral HDsEMG recordings of the tibialis anterior (TA) were performed to assess MU characteristics, including MUDR and MUDR variability. In brief, MUDR was defined as the mean firing frequency during a 10-second plateau at 25% MVC, while MUDR variability was calculated as the coefficient of variation of inter-spike intervals. For a full description of these methods, see chapter 3.2.4.6.

5.3.4 Statistical analysis

Statistical analyses were performed in RStudio (v4.4.3).

Within-stroke analyses: To evaluate limb-based effects while accounting for repeated measurements and nested MU data, linear mixed-effects models (LMMs) were implemented using the lme4 package (Bates et al., 2015). Models included fixed effects of leg (paretic vs non-paretic) and their interaction with measurement variables, with

participants specified as random intercepts. Random slopes were included where supported by model fit.

Between-group comparisons: To compare stroke participants with age-matched healthy controls, separate LMMs were fitted including group (stroke vs control), leg (paretic/non-paretic or dominant/nondominant), and their interaction as fixed effects. This allowed assessment of main group effects and group × leg interactions on MVC, force steadiness, force-tracking accuracy, and motor-unit discharge parameters. When appropriate, follow-up comparisons were conducted using the emmeans package (Lenth and Lenth, 2018).

All data are reported as Estimated Marginal Means (EMMs) with 95 % confidence intervals. Model assumptions were verified by visual inspection of residuals. Statistical significance was set at $p < 0.05$.

5.4 Results

5.4.1 Participant characteristics

Ten stroke survivors and sixteen healthy participants were included in the study. A summary of their demographic and clinical characteristics is provided in Table 5.1. There were no significant differences in age, height, weight, or BMI between the two groups, although the sex distribution was uneven.

Table 5.1 Participants' characteristics

Characteristic	**Stroke patients (n=10)**	**Healthy volunteers (n=16)**	**p-value**
Age (years)	70.4 (16)	73.8 (5.1)	0.52
Sex (M/F)	4/6	8/8	___
Height (cm)	165.8 (0.08)	166.7 (6.8)	0.60
Weight (kg)	82.4 (23)	73.9 (10.4)	0.29
BMI (kg/m^2)	29.8 (8.2)	26.6 (2.7)	0.25
Stroke type (Isch/Haem)	10/0	___	___
Time since stroke (months)	34.5 (17.8)	___	___

Affected side (R/L)	6/4	___	___
Modified Rankin Scale	2 [2-3]	___	___

Data are presented as mean (standard deviation) unless otherwise indicated; Modified Rankin Scale values are shown as median [interquartile range]. Abbreviations: M/F, male/female; BMI, body mass index; Isch, ischaemic; Haem, haemorrhagic; R/L, right/left. Between-group comparisons were performed using independent-samples t-tests Statistical significance was set at $p < 0.05$.

5.4.1.1 Stroke impact scale

Patients' self-reported stroke impact can be seen in Table 5.2. Based on clinical guidelines and prior studies, this data indicates a moderate level of perceived disability across multiple functional domains. Strength, hand function, mobility, and ADL/IADL all demonstrated reduced scores, with hand function being the most affected domain (mean score: 43.5 ± 31.9). Emotion, memory and thinking, and communication domains were relatively preserved, consistent with previous findings that cognitive and emotional domains often recover better than physical function post-stroke. Participation scores were also low (55.5 ± 32.0), suggesting ongoing limitations in social and role engagement. The mean global recovery score (60 ± 15.6) reflects partial but incomplete perceived recovery, reinforcing the long-term impact of stroke on quality of life.

Table 5.2 Mean Stroke Impact Scale scores (n=10)

SIS Domain	Mean score	Score range
Strength	66.1 (21.2)	25-96
Hand Function	43.5 (31.9)	0-100
Mobility	63.2 (20.1)	33-92
ADL/IADL	62.3 (22)	30-96
Emotion	82.4 (15.3)	58-100
Memory & Thinking	77.8 (18.5)	32-100
Communication	77 (24.6)	30-100
Participation/Role	55.5 (32)	0-100
Global Recovery (0–100)	60 (15.6)	30-80

Data shown as mean (standard deviation). Abbreviations: ADL/IADL, Instrumental/Activities of Daily Living.

5.4.1.2 Fugl-Meyer assessment

Post-stroke motor impairment can be seen in Table 5.3. Based on clinical thresholds, this indicates mild upper-limb and moderate lower-limb motor impairment, with variability in recovery levels. These functional scores were utilised to stratify motor severity and guide the analysis of neuromuscular performance.

Table 5.3 Fugl-Meyer Assessment scores

FMA Domain	Mean score	Score range
FMA-UE	46.6 (15.8)	22-66
FMA-LE	28.1 (5.1)	20-34

Data shown as mean (standard deviation). Abbreviations: FMA, Fugl-Meyer Assessment; UE, Upper Extremity; LE, Lower Extremity.

5.4.2 Isometric strength

For MVC, there was a significant group x leg interaction (p=0.002) and a significant main effect of group, with MVC approximately 70N higher in the control group compared to the stroke patients (p<0.001). There was no significant main effect of leg (Figure 5.5); however, EMMs showed the group x leg interaction was explained by a significant bilateral difference in the stroke group (p=0.02), which was not apparent in the controls (p=0.99).

Table 5.4 Ankle dorsiflexors maximum voluntary contraction (MVC)

Group	Leg	Mean (N)	SD	95% CI	Difference within group
Control	Favoured	175	40	[153.7, 196.3]	—
	Non-favoured	178	42	[155.6, 200.4]	+3 N (ns, p = 0.99)
Stroke	Favoured	125	35	[99.9, 150.1]	—
	Non-favoured	108	32	[85.1, 130.9]	−17 N ↓ (p = 0.02)

Abbreviations: N*, Newtons; SD, standard deviation; CI, confidence intervals.*

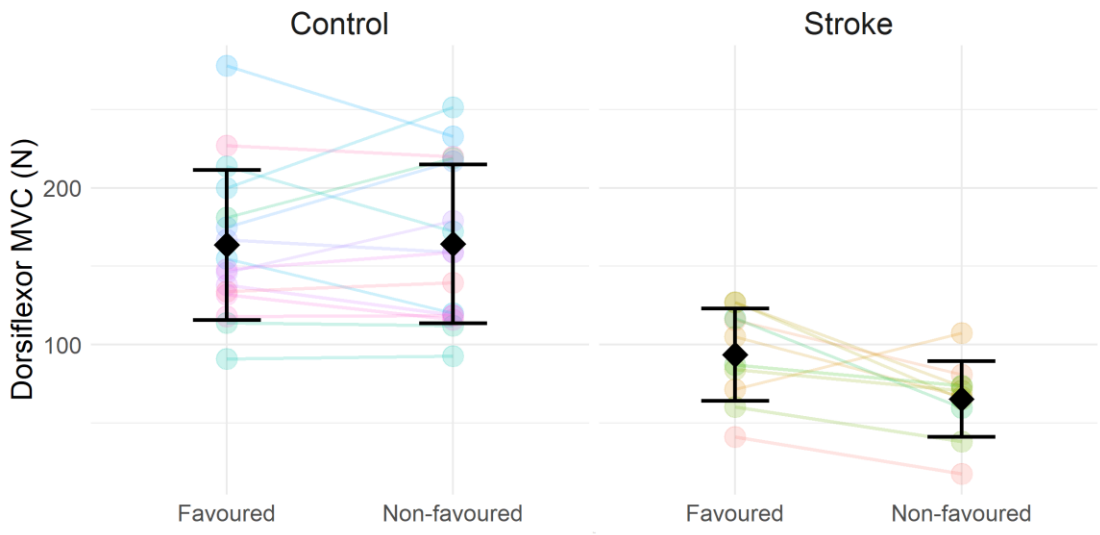


Figure 5.5 Ankle dorsiflexor maximum voluntary contraction (MVC; newtons (N)) in stroke survivors and healthy controls, comparing their favoured and non-favoured limbs. Black diamonds represent group means, black error bars indicate standard deviations (SD), and coloured circles show individual participant values, with lines connecting data from the same participant across limbs.

5.4.3 Motor control

For FS, there was a significant group × leg interaction ($p<0.001$), but no main effect of group ($p=0.36$) or leg ($p=0.20$) (Figure 5.6). EMM's showed the group x interaction was explained by a significant bilateral difference in the stroke group ($p<0.001$), which was not observed in the control group ($p=0.56$). The non-favoured limb in the stroke group had a markedly higher CoV (25.0%) compared to the favoured side (12.3%) ($p<0.001$), indicating reduced FS. In contrast, the control group showed similar values across limbs (favoured: 7.8%; non-favoured: 5.0%) ($p= 0.55$).

Table 5.5 Ankle dorsiflexors force steadiness (FS)

Group	Leg	Mean(CoV)	SD	95% CI	Difference within group
Control	Favoured	0.078	0.030	[0.062, 0.094]	—
	Non-favoured	0.050	0.025	[0.036, 0.063]	−0.028 ↓ (p = 0.55, ns)
Stroke	Favoured	0.123	0.045	[0.091, 0.155]	—
	Non-favoured	0.250	0.090	[0.186, 0.314]	+0.127 ↑ (p < 0.001)

Abbreviations: CoV, *coefficient of variation; SD, standard deviation; CI, confidence intervals.*

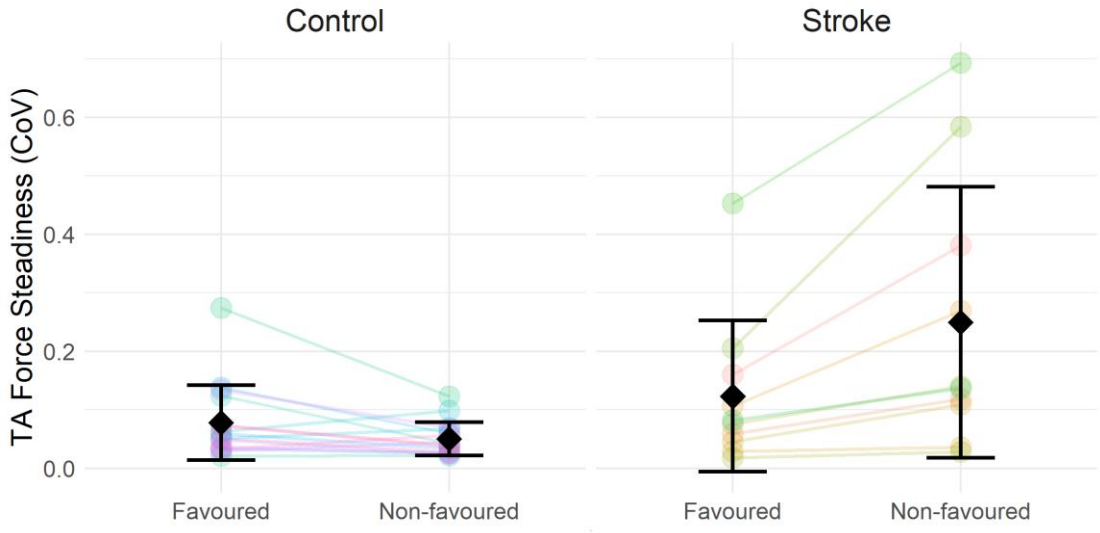


Figure 5.6 Tibialis anterior (TA) force steadiness (coefficient of variation (CoV)) in stroke survivors and healthy controls, comparing their favoured and non-favoured limbs. Higher CoV represents poorer force steadiness. Black diamonds represent group means, black error bars indicate standard deviations (SD), and coloured circles show individual participant values, with lines connecting data from the same participant across limbs.

For CC of the sinewave tracking (complex force tracking), there was no significant group × leg interaction ($p=0.38$) and no main effect of leg ($p=0.58$). There was, however, a significant main effect of group, with CC approximately 0.27 higher in the control group than in stroke participants ($p=0.001$) (Figure 5.7A).

For AUC of the sinewave tracking, which represents the total deviation of the produced force from the target waveform over the tracking period, with higher values indicating greater overall tracking error, there was no significant group × leg interaction ($p=0.25$) and no main effect of leg ($p=0.90$). As with CC, there was a significant main effect of group, with AUC approximately 4.27 units higher in the stroke group compared to controls ($p<0.001$) (Figure 5.7B).

Table 5.6 Ankle dorsiflexors sinewave force tracking accuracy (FTA)

Correlation coefficient

Group	Leg	Mean (CC)	SD	95% CI	Difference within group
Control	Favoured	0.80	0.09	[0.732, 0.828]	—
	Non-favoured	0.78	0.08	[0.757, 0.843]	+0.02 (ns, p = 0.58)
Stroke	Favoured	0.51	0.16	[0.395, 0.625]	—
	Non-favoured	0.48	0.15	[0.372, 0.588]	−0.03 (ns, p = 0.38)

Area under the curve

Group	Leg	Mean (AUC)	SD	95% CI	Difference within group
Control	Favoured	1.75	0.70	[1.38, 2.12]	—
	Non-favoured	1.68	0.65	[1.33, 2.03]	−0.07 (*ns, p* = 0.90)
Stroke	Favoured	6.03	2.10	[4.53, 7.53]	—
	Non-favoured	7.01	2.40	[5.29, 8.73]	+0.98 (*ns, p* = 0.25)

Abbreviations: CC*, correlation coefficient; AUC, area under the curve; SD, standard deviation; CI, confidence intervals.*

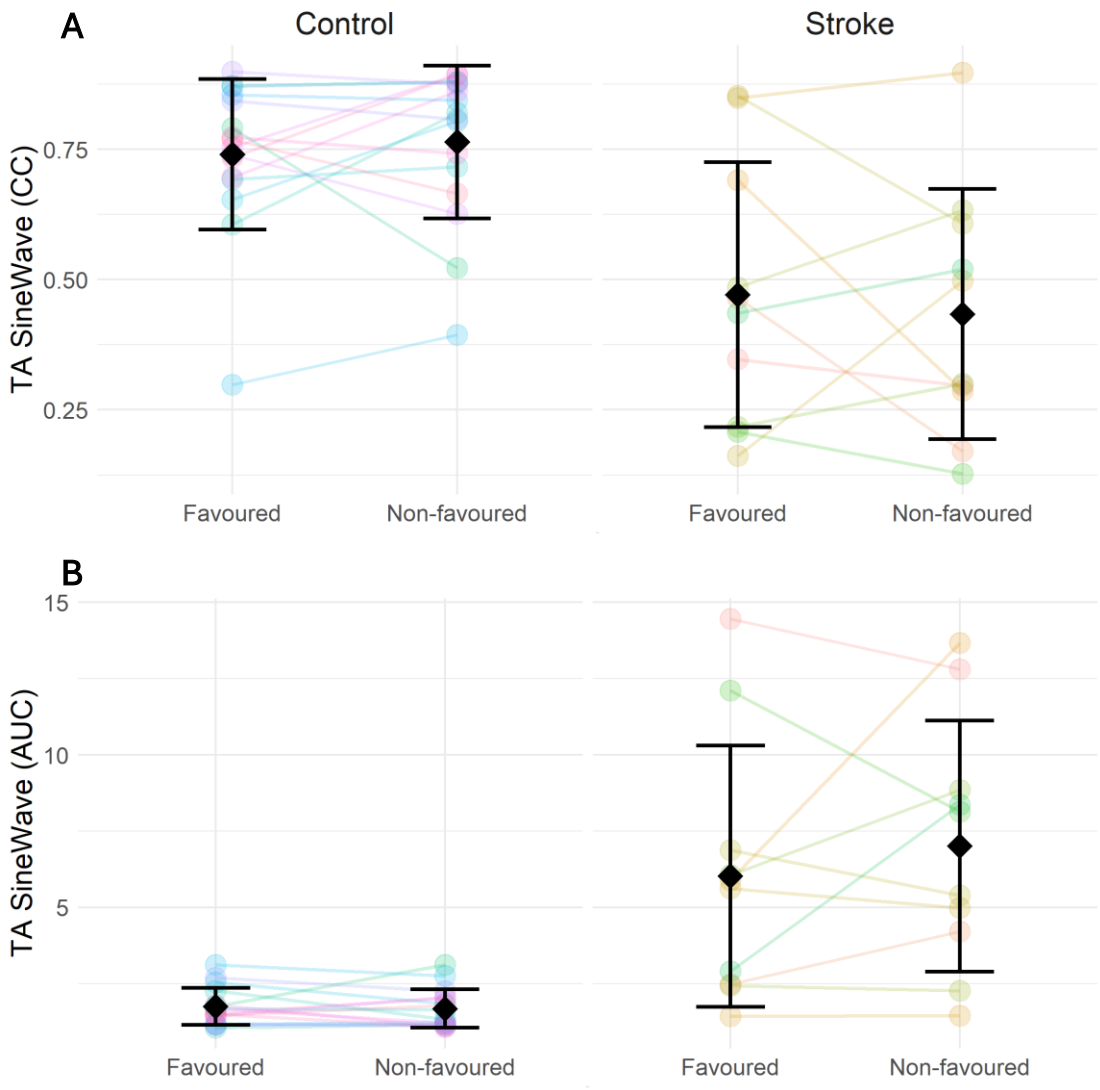


Figure 5.7 A) Correlation coefficient (CC) and B) area under the curve (AUC) of the sinewave task in stroke survivors and healthy controls, comparing their favoured and non-favoured limbs. Abbreviations: TA, tibialis anterior. Lower CC and higher AUC represent poorer motor control. Black diamonds represent group means, black error bars indicate standard deviations (SD), and coloured circles show individual participant values, with lines connecting data from the same participant across limbs.

5.4.4 High-density surface electromyography (HDsEMG)

For TA MUDR, there was a significant group x leg interaction ($p=0.002$), a significant main effect of leg ($p<0.001$), but no main effect of group ($p=0.60$). EMMs showed the group x leg interaction was explained by a greater bilateral difference in the stroke group;

~1.75pps greater in the favoured (p<0.001), whereas the controls showed only a ~0.78 greater MUDR in the dominant limb (p=0.002) (Figure 5.8A).

For TA MUDR variability, there was no significant interaction (p=0.68), and no main effect of leg (p=0.51). There was, however, a main effect of group, with CoV 7.2% higher in the stroke group, when compared to controls (p=0.04) (Figure 5.8B).

Table 5.7 Tibialis anterior (TA) motor units discharge rate (MUDR) and variability

Discharge rate

Group	Leg	Mean (pps)	SD	95% CI	Difference within group
Control	Favoured	13.5	2.1	[12.38, 14.62]	—
	Non-favoured	12.7	2.0	[11.63, 13.77]	−0.8 ↓ (p = 0.002)
Stroke	Favoured	11.8	2.0	[10.37, 13.23]	—
	Non-favoured	10.0	2.0	[8.57, 11.43]	−1.8 ↓ (p < 0.001)

Discharge rate variability

Group	Leg	Mean (CoV)	SD	95% CI	Difference within group
Control	Favoured	0.20	0.06	[0.16, 0.23]	—
	Non-favoured	0.21	0.06	[0.17, 0.24]	+0.01 (*ns, p* = 0.51)
Stroke	Favoured	0.27	0.08	[0.21, 0.32]	—
	Non-favoured	0.28	0.08	[0.22, 0.33]	+0.01 (*ns, p* = 0.68)

Abbreviations: pps*, pulses per second; CoV, coefficient of variation; SD, standard deviation; CI, confidence intervals.*

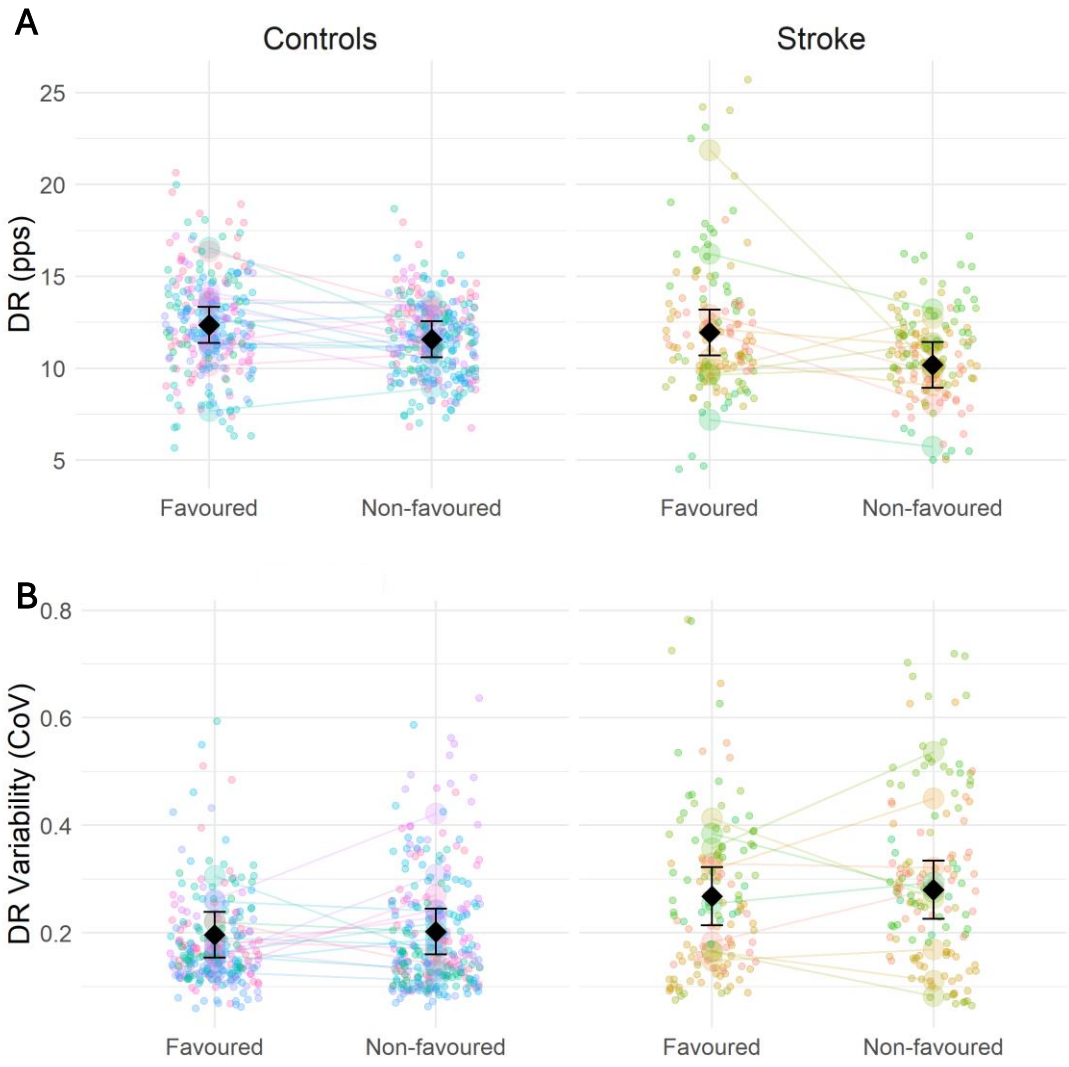


Figure 5.8 A) Tibialis anterior (TA) discharge rate; and B) TA discharge rate (DR) variability of stroke survivors and healthy controls comparing their favoured and non-favoured limbs. Abbreviations: pps, pulse per second; CoV, coefficient of variation. Black diamonds and error bars represent estimated marginal means and 95% CI from model outputs. Large, coloured circles show individual participant means, with lines connecting data from the same participant across limbs, and small coloured circles show individual motor unit values, colour-coded to participant.

5.5 Discussion

This chapter explored bilateral neuromuscular function in stroke survivors, comparing their paretic and non-paretic limbs with the dominant and non-dominant limbs of healthy older adults. The key findings are significant neuromuscular impairments post-stroke, including

reduced strength and impaired force control, both of which appear to be underpinned by profound alterations in MU behaviour as revealed by HDsEMG analysis. Notably, the presence of bilateral deficits (i.e., lower MVC, poorer FTA, and increased MUDR variability in both limbs compared to controls) suggests that stroke-related impairments extend beyond the clinically affected side, with implications for future rehabilitation strategies.

Our findings confirm that stroke survivors exhibit significantly lower strength in both limbs compared to healthy controls, consistent with a substantial body of previous literature demonstrating profound post-stroke muscle weakness (Li et al., 2014, Dragert and Zehr, 2013). Interestingly, although the paretic limb displayed the most pronounced strength deficits, the non-paretic limb also demonstrated weakness relative to the values seen in healthy controls, suggesting widespread neuromuscular impairment rather than side-specific deficits. This observation aligns with recent work on bilateral force control and gait (Patel and Lodha, 2025), progressive contralesional cortico-reticulospinal pathway recruitment (Taga et al., 2024), and diminished corticomuscular coherence across limbs post-stroke (Gao et al., 2024), supporting the role of bilateral corticospinal and brainstem pathway disruption (Beauchamp et al., 2023, Li et al., 2014). These findings challenge the traditional view of unilateral deficits post-stroke and support evidence of bilateral neuromuscular involvement after unilateral cortical injury.

Based on work in more recent years (e.g., (Horstman et al., 2008, Wareńczak-Pawlicka and Lisiński, 2025, Bowden et al., 2014), bilateral strength deficits post-stroke are now relatively well-documented, with suggestions that these are due to both direct effects (i.e., impaired descending corticospinal drive and altered motor unit recruitment) (Taga et al.,

2024, Casula et al., 2021) and indirect effects (i.e., reduced contractile activity and disuse-related muscle atrophy) (Beauchamp et al., 2023, Ryan et al., 2002).

Although Horstman et al. (2008) assessed intrinsic muscle strength and voluntary activation in both lower limbs of individuals post-stroke, demonstrating significant bilateral strength reductions and associations with impaired functional performance, they did not investigate the underlying MU behaviour contributing to this weakness. Similarly, Wareńczak-Pawlicka & Lisiński (2025) examined the paretic and non-paretic lower limbs in post-stroke patients, finding substantial bilateral deficits in maximal force and voluntary activation. However, as their analysis was based on whole-muscle measures, without the use of HDsEMG, their conclusions were limited to central activation failure at the global muscle level. Consistent with this interpretation, recent HDsEMG studies have demonstrated stroke-related alterations in MU discharge behaviour in both distal and proximal muscles and have linked MU discharge changes to functional performance (Negro et al., 2020, Murphy et al., 2015).

Herein, the HDsEMG data provide novel evidence that increased MUDR variability in both limbs post-stroke may contribute mechanistically to the observed weakness, representing one of the first demonstrations of a direct link between altered MU discharge characteristics and bilateral strength loss in this population.

FS showed a significant group × leg interaction, with stroke survivors demonstrating poorer FS in the non-favoured limb compared to their favoured limb, whereas no bilateral difference was observed in controls. Force steadiness reflects the ability to maintain a constant force output over time, which depends on the precise and consistent recruitment and discharge of MUs, as well as adequate sensory feedback to modulate output. Poor FS

is typically manifested as greater fluctuations in force around a target level, indicating increased neuromuscular noise and reduced motor control precision (Enoka and Farina, 2021).

Reductions in FS have been shown to be a feature of advancing age, with older adults exhibiting greater fluctuations in submaximal force output compared to younger individuals (Enoka et al., 2003, Tracy et al., 2005a). Similar impairments have been reported in neurological conditions, including Parkinson's disease (Romanato et al., 2022, Christou et al., 2003, Skinner et al., 2019) and multiple sclerosis (Carroll et al., 2011, Pethick and Tallent, 2022). FS deficits are also evident in musculoskeletal disorders, such as anterior cruciate ligament injury (Alnahdi et al., 2012, Pethick et al., 2022a) and following periods of prolonged limb immobilisation (Clark et al., 2008, Pethick and Tallent, 2022). These impairments are clinically significant, as poor FS has been linked to reduced balance control, impaired gait stability, and increased risk of falls (Laidlaw et al., 2000, Welsh et al., 2007).

Although the favoured limb of our stroke survivors was less affected than the non-favoured limb, it still demonstrated reduced FS compared to healthy controls. This finding aligns with prior work showing that both the paretic and non-paretic limbs in stroke survivors exhibit impaired force control during isometric tasks (Chow and Stokic, 2013), supporting the hypothesis that bilateral neural dysfunction may occur secondary to interhemispheric disinhibition or compensatory reorganisation (Beauchamp et al., 2023). Mechanistically, chronic stroke has been associated with impaired modulation of MUDR during synergy-driven contractions of the biceps brachii (Beauchamp et al., 2023), indicating altered descending drive and disrupted motor control strategies that could contribute to reduced steadiness in both limbs.

Importantly, FS appears to be modifiable; targeted neuromuscular interventions such as low-load force training, resistance training, and motor skill practice have been shown to improve steadiness by reducing MU discharge variability and enhancing sensorimotor integration (Patel et al., 2021, Vila-Chã and Falla, 2016, Lin et al., 2024). Our concomitant observations of impaired FS and MU-level alterations therefore provide a novel mechanistic explanation for functional instability in stroke survivors and highlight FS as a potential therapeutic target for rehabilitation.

In terms of the day-to-day impacts of this, reduced FS may translate into difficulties with tasks requiring controlled and sustained muscle activation, such as holding a cup without spilling, climbing stairs smoothly, buttoning clothing, or maintaining a steady grip on walking aids. These seemingly small deficits can accumulate to limit independence, increase fatigue, and elevate fall risk, all of which negatively affect quality of life (Patel et al., 2021, Blomkvist et al., 2018).

In addition to reduced strength and FS, stroke survivors also exhibited impaired sinusoidal tracking performance compared to healthy controls. This task requires participants to continuously modulate force in synchrony with a changing target, engaging both feedforward motor planning and real-time sensory feedback to adjust output. As such, poorer performance reflects reduced dynamic neuromuscular coordination, diminished capacity to scale force smoothly, and impaired integration of proprioceptive and visual feedback. These deficits are consistent with prior evidence of disrupted proprioceptive processing and cortical motor planning post-stroke (Chow and Stokic, 2013) and may manifest functionally as difficulty in activities that require graded or alternating muscle

activation, such as controlling grip strength when pouring a drink, pacing steps when walking on uneven terrain, or adjusting pressure when using tools.

Although these impairments are well recognised and have been previously reported in the literature, this study is among the first to demonstrate that altered MU discharge precision contributes to impaired coordination. Specifically, HDsEMG analysis revealed increased variability in MUDR, offering a neural explanation for these functional deficits.

Our data suggests global deficits in complex force control across both limbs of stroke survivors. This aligns with robust existing evidence of bilateral cortical reorganisation post-stroke, including dynamic hemispheric motor network changes during recovery (Du et al., 2022), restored bilateral primary motor cortex functional connectivity following repetitive transcranial magnetic stimulation interventions (Cheng et al., 2023), and structural sensorimotor cortex remapping post-stroke (Eckert, 2024). Collectively, these findings and those reported herein underscore the need for stroke rehabilitation interventions that target both the paretic and non-paretic limbs to address bilateral motor dysfunction (Kim et al., 2025, Hendy and Lamon, 2017).

HDsEMG measures revealed lower MUDR in the paretic limb of stroke survivors, consistent with impaired descending drive and motoneuron excitability (Li et al., 2014). Interestingly, the non-paretic limb exhibited slightly elevated MUDR compared to controls, potentially reflecting compensatory contralesional cortical drive (Mesquita et al., 2024, Manca et al., 2018).

Such compensatory increases may also contribute to maladaptive interhemispheric inhibition, whereby excessive contralesional primary motor cortex (M1) output suppresses ipsilesional M1 activity and limits paretic limb recovery (Calvert and Carson, 2022, Palmer

et al., 2019, Casula et al., 2021). This highlights the complex neural dynamics governing bilateral motor control after stroke. These findings underscore the importance of interventions targeting motoneuron excitability and firing regularity to restore function.

Notably, increased MUDR variability was evident in both limbs of stroke survivors, suggesting widespread synaptic noise and impaired neuromodulatory control. These findings provide novel mechanistic insight into the neural basis of bilateral deficits in stroke, moving beyond functional observations to characterise MU-level dysfunction directly.

The HDsEMG analysis presented in this chapter represents a significant advancement in stroke research, demonstrating that altered MU discharge behaviour is not confined to the clinically affected limb but extends bilaterally.

A novel aspect of this study was the focus on group × limb interactions to assess asymmetry, with a large body of previous literature in stroke patients only focussed on the function of the paretic limb (Wareńczak-Pawlicka and Lisiński, 2025, Kitsos et al., 2013). For strength and FS, significant group × limb interactions indicated greater asymmetry in stroke survivors than in controls, with, as expected, the paretic limb being disproportionately affected. However, some measures, such as complex force control, revealed main effects of group without significant limb differences, suggesting that specific neural deficits (i.e., those at the MU level) may generalise across both sides (Patel and Lodha, 2025).

These results align with previous findings of bilateral corticospinal reorganisation following unilateral stroke and support the hypothesis that even the non-paretic limb may not be functionally “normal” (Hendy and Lamon, 2017, Patel and Lodha, 2025). Such

bilateral involvement has critical implications for rehabilitation, suggesting that both limbs should be targeted during rehabilitation therapy to maximise recovery and minimise functional asymmetries. Functional asymmetries after stroke have been associated with slower performance and reduced efficiency in activities of daily living (Yadav et al., 2019), impaired bimanual coordination (Waller and Whitall, 2008), and an increased reliance on compensatory strategies that may limit motor recovery (Lang et al., 2005). Over time, preferential use of the less-affected limb can also contribute to overuse injuries and secondary musculoskeletal disorders in that limb (Mani, 2013). Collectively, these findings emphasise the importance of bilateral assessment and training in post-stroke rehabilitation to restore functional balance and reduce the long-term consequences of asymmetrical limb use.

Our findings of bilateral deficits in stroke survivors resonate with the concept of cross-education; whereby unilateral training can induce neural adaptations in the contralateral limb (Green and Gabriel, 2018b). Given that MU behaviour is altered bilaterally, interventions leveraging cross-education and targeting MU firing regularity may be particularly effective in stroke rehabilitation. More specifically, unilateral FAT and/or similar low-load interventions could via cross-education, promote neural plasticity in the stroke-affected limb, even in patients unable to actively engage their paretic limb (Hendy and Lamon, 2017, Lecce et al., 2025). Of note, interventions incorporating eccentric resistance training appear particularly promising, offering robust cross-education effects and the ability to induce neural adaptations in untrained muscles (Lecce et al., 2025).

Evidence suggests cross-education effects are mediated by increased corticospinal excitability, interhemispheric facilitation, and cortical reorganisation (Calvert and Carson, 2022, Urbin et al., 2015a); mechanisms which could be exploited during unilateral

rehabilitation to achieve cross-education. Indeed, based on the changes in MVC and FS shown with FAT in chapters 2 and 3 of this thesis, unilateral FAT may, via cross-education, represent a novel, clinically relevant strategy for restoring bilateral motor symmetry after stroke. These approaches could be especially beneficial for stroke survivors with severely impaired paretic limbs, allowing indirect functional improvements via the non-paretic side.

A key strength of this study was the use of HDsEMG to quantify MU discharge behaviour, providing mechanistic insights into neural dysfunction post-stroke, an area with limited prior research, particularly in lower limb muscles. Most existing work in this field has used conventional surface EMG or intramuscular EMG and has predominantly focused on upper limb muscles such as the biceps brachii or first dorsal interosseous (Li et al., 2014, Beauchamp et al., 2023). Only a small number of studies have applied HDsEMG decomposition to post-stroke populations, and these have primarily examined voluntary contractions in the upper limb (Negro et al., 2016, McManus et al., 2017). Consequently, MU-level analyses of lower limb motor control post-stroke remain scarce, and our inclusion of the tibialis anterior provides novel insight into the bilateral neuromuscular consequences of stroke. The inclusion of an age-matched healthy comparison group allowed differentiation between deficits due to normal ageing and those attributable to stroke. However, the relatively small sample size limits generalisability. In addition, the sample composition may influence the applicability of findings, as sex-related differences in neuromuscular characteristics have been reported in older adults, with males generally demonstrating higher absolute strength but differing patterns of motor unit remodelling and fatigability compared to females (Guo et al., 2025, Jones et al., 2022). Furthermore, all stroke participants in this study had an ischaemic stroke, and findings may not be directly

transferable to haemorrhagic stroke populations, where lesion characteristics and recovery trajectories can differ (Meschia and Brott, 2018). Our cohort's mean age was comparable to that of controls; this selection strategy may not represent the broader post-stroke population, which includes younger survivors. As such, the findings should be considered within the context of a pilot/exploratory study, aimed at assessing the additional impact of stroke beyond ageing, rather than as a fully representative epidemiological sample. Although it is almost impossible to assess actual reductions in function after stroke (i.e., compared to before) due to the unpredictable nature of the event, and given that we did not control for stroke vintage (time since stroke), which may influence neuromuscular recovery profiles, longitudinal studies assessing neuromuscular changes over the course of stroke recovery are warranted.

A limitation of this study is that it was not registered or conducted as a formal randomised controlled or case–control trial. The healthy control participants were included as a reference group for comparison, but not as part of a prospectively registered control arm. While this design was sufficient for cross-sectional comparison of neuromuscular characteristics, a case–control or matched longitudinal design could provide stronger causal inference regarding stroke-related neural adaptations and rehabilitation outcomes. Future studies should therefore adopt a controlled design with pre-registered comparator groups to strengthen generalisability.

The study was powered to detect large stroke-related differences in FS relative to controls. Although this provided sufficient sensitivity for gross between-group effects, the design was not powered for smaller or more subtle limb-to-limb differences within the stroke group. Because such comparisons are exploratory, future work should employ formal power analyses based on variance estimates from the current dataset.

The stroke survivor sample in this study was relatively small and may not fully represent the broader stroke population. The inclusion criteria required participants to be able to perform voluntary isometric contractions and follow task instructions, which likely favoured individuals with mild-to-moderate impairments and excluded those with severe cognitive or motor deficits. As a result, the range of functional and neural impairments captured may underestimate the full spectrum of post-stroke disability.

In addition, the cohort comprised chronic stroke survivors, with an average time since stroke exceeding two years. This extended post-stroke period may have influenced the findings, as prolonged disuse and compensatory neural reorganisation can exacerbate muscle weakness and bilateral motor-unit dysfunction, independent of the initial lesion severity. Consequently, the results should be interpreted within the context of a chronic, relatively high-functioning stroke population. Future studies should include more heterogeneous samples, including individuals in subacute stages of recovery, to capture the evolution of bilateral neural adaptations across different recovery timelines.

Future research should explore whether FAT or other low-load neuromuscular interventions can restore MU discharge consistency and contractile function after stroke, and whether such adaptations can be achieved via CE.

This study provides evidence that stroke survivors exhibit profound neuromuscular impairments in both limbs, with altered force control, MU discharge behaviour, and reduced strength relative to healthy older adults. Bilateral deficits highlight the importance of considering both paretic and non-paretic limbs in rehabilitation planning. Interventions

leveraging neural plasticity and cross-education, such as FAT, may offer promising avenues to improve functional recovery and reduce asymmetry in this population.

Chapter 6: Discussion

6.1 Overview of Aims

The overarching purpose of this thesis was to investigate neuromuscular adaptations to low-load motor control exercise interventions in older adults, and to explore the potential

relevance of these adaptations for stroke survivors. This work was motivated by recognition that neuromuscular declines associated with age and stroke cannot be fully addressed by 'traditional' high-load resistance exercise training (RET) alone, as many older adults and clinical populations cannot tolerate high mechanical loads due to joint pathology, cardiovascular risk, or frailty (Phillips and Winett, 2010, Fragala et al., 2019). Novel approaches targeting neural adaptation, such as force accuracy training (FAT) or exploitation of somewhat understudied physiological phenomena (i.e., cross-education (CE)), may offer accessible, clinically relevant alternatives (Hendy and Lamon, 2017, Manca et al., 2018).

To address these gaps, the thesis was structured around five interlinked aims. The first aim was to systematically evaluate the existing evidence for CE of lower limb strength following unilateral RET, providing a synthesis of effect sizes and addressing methodological considerations, and the neural mechanisms proposed to underpin this phenomenon. This was achieved through a published systematic review and meta-analysis (Chapter 2).

The second and third aims were to determine neuromuscular adaptations to unilateral FAT in healthy older adults, using high-density surface electromyography (HDsEMG) to examine changes in motor unit (MU) behaviour, force steadiness (FS), and force-tracking accuracy (FTA). These aims also included a comparison of adaptations in proximal (vastus lateralis (VL), Chapter 3) versus distal (tibialis anterior (TA), Chapter 4) lower limb muscles, enabling a muscle-specific analysis of FAT-induced neural plasticity.

The fourth aim was to evaluate the extent of CE from unilateral FAT via assessment of a contralateral untrained limb, and to assess the retention of these adaptations following a period of detraining. This was integrated into the experimental studies in Chapters 3 and 4.

Finally, the fifth aim was to characterise bilateral neuromuscular impairments in stroke survivors compared to age-matched healthy older adults (Chapter 5). This descriptive analysis provided a direct comparison between age and stroke-related neural changes and considered the potential applicability of FAT and the role of CE in stroke rehabilitation.

Collectively, the studies performed to achieve these aims sought to establish a mechanistic understanding of how neural-targeted exercise interventions can influence MU behaviour in older adults and provide translational insights for populations with unilateral neuromuscular deficits, such as stroke survivors.

6.2 Summary of Key Findings

This thesis generated several novel insights into the neural and functional adaptations elicited by low-load, motor control interventions in older adults, and into the neuromuscular characteristics of stroke survivors.

From the systematic review and meta-analysis, it was concluded that unilateral RET elicits significant CE with regard to lower limb strength, with pooled effect sizes indicating contralateral strength gains of moderate magnitude, consistent with previous work in the upper limbs (Carroll et al., 2006a, Lee and Carroll, 2007a). Further, these gains occurred without hypertrophy in the untrained limb, supporting a neural basis for CE (Kidgell et al., 2015b). Importantly, methodological exploration revealed that training modality, contraction type, and programme duration each influenced the magnitude of CE, with eccentric contractions and higher-intensity protocols eliciting the greatest effects (Manca et al., 2018). However, evidence in older adults remains uncommon, particularly for lower limb muscles, highlighting a clear research gap addressed in this thesis.

The experimental studies in ‘healthy’ older adults demonstrated that four weeks of unilateral FAT induced measurable improvements in FS, FTA, and specific aspects of MU

behaviour in both the trained and untrained limbs. In the VL, FAT reduced MU discharge rate (MUDR) variability and improved submaximal FS, effects that were partially retained after two weeks of detraining. CE effects were also observed, with the untrained limb showing parallel improvements in FS and reductions in MUDR variability. In the TA, FAT elicited broadly similar neural adaptations to the VL, including enhanced FS and reduced MUDR variability, but the magnitude of change was generally smaller than in the VL. These specific differences suggest that muscle location and habitual use may modulate the responsiveness of MUs to neural-targeted interventions in older adults as previously reported (Kilroe et al., 2019). Across both muscles, changes in neural parameters were observed in the absence of any muscle size measurements in the present studies. While hypertrophy was not directly assessed, the short intervention duration and the low mechanical loading used make it unlikely that structural adaptations accounted for the observed improvements. This interpretation aligns with previous findings that FAT and other low-load, skill-based interventions primarily elicit central rather than peripheral adaptations (Mitchell et al., 2012a, Kidgell and Pearce, 2011).

The comparative study of stroke survivors and age-matched controls revealed that neuromuscular impairments in stroke extend beyond the paretic limb. HDsEMG analysis confirmed substantial reductions in MUDR in the paretic limb, alongside increased MUDR variability. Notably, the non-paretic (favoured) limb also exhibited significant deficits in FS and MUDR variability compared to healthy controls, supporting the hypothesis of bilateral corticospinal involvement after stroke (Beauchamp et al., 2023). These findings provide mechanistic support for interventions that address both limbs, rather than focusing solely on the paretic side.

Collectively, these findings demonstrate that FAT is an effective, low-load intervention capable of improving neuromuscular function in older adults, with evidence of cross-limb transfer and short-term retention of adaptation. The data from stroke survivors highlight the potential translational value of FAT in clinical rehabilitation, particularly for populations unable to tolerate high-load bilateral training.

6.3 Concluding Remarks

Taken together, the studies in this thesis go some way towards addressing the knowledge gaps identified at the outset. They demonstrate that FAT can induce MU-level adaptations and CE in older adults, expanding the lower-limb CE evidence base for this population. They provide the first comparative analysis of FAT responses between proximal and distal muscles, offering insight into muscle-specific neural plasticity. They also document bilateral neuromuscular deficits in stroke survivors, challenging the traditional focus on the affected limb in rehabilitation.

Conceptually, the integration of FAT and CE represents a departure from conventional high-load RET paradigms, offering a framework for interventions that prioritise neural plasticity over muscle hypertrophy. Such strategies could be particularly valuable for frail individuals or those with limited exercise tolerance, for whom high-mechanical-load programmes are not feasible.

By applying identical HDsEMG methodologies to both healthy older adults and stroke survivors, this work offers a mechanistic bridge between age-related and stroke-related neuromuscular decline. The findings support the emerging shift in rehabilitation science towards interventions that optimise neural control, an approach shown here to yield functional gains without hypertrophy, consistent with other low-load or skill-based training research (Mitchell et al., 2012a, Kidgell and Pearce, 2011). This perspective has clear

translational potential for older populations and for clinical contexts such as stroke, where time-efficient, accessible, and low-risk interventions are needed.

6.4 Strengths and limitations

This thesis has several methodological and conceptual strengths. Across all experimental chapters, identical measurement protocols were used, including (HDsEMG), standardised force-tracking tasks, and harmonised data-processing procedures. This consistency ensured high internal validity and allowed for direct comparison of neuromuscular adaptations across muscle groups (Chapters 3 and 4) and populations (older adults vs. stroke survivors, Chapter 5). The integration of quantitative HDsEMG analysis with functional outcomes (e.g., FS, FTA, general mobility) provided a comprehensive assessment of neural and behavioural adaptations. Furthermore, by combining a systematic review, two mechanistic training studies, and a clinical observational study within one body of work, the thesis delivers a clear translational continuum, from theory and mechanism to potential clinical application.

Despite these strengths, several limitations must be acknowledged. Sample sizes in the experimental studies were modest, reflecting the intensive nature of HDsEMG testing and analysis. Also, the time commitment is required for repeated training and detraining assessments. Although power calculations indicated adequate sensitivity for large effects, smaller or more subtle neural adaptations may have been undetected. The older-adult participants were functionally independent and relatively healthy, which may limit generalisability to frailer or multimorbid populations.

The stroke cohort, while carefully characterised, was also limited in representativeness. Inclusion criteria requiring voluntary control and comprehension likely excluded those with severe impairments, resulting in a mild-to-moderate sample. Moreover, the average time

since stroke exceeded two years, meaning participants were in the chronic phase of recovery; therefore, the results may reflect adaptations associated with long-term disuse or neural reorganisation rather than acute or subacute processes. The observational design and cross-sectional comparisons preclude causal inference regarding neural mechanisms.

Finally, while FAT was shown to enhance MU behaviour and functional control, the short intervention duration (4 weeks) restricts conclusions about long-term persistence or translation to clinical rehabilitation outcomes such as falls or daily function. Future large-scale and longitudinal studies are needed to confirm the durability and applicability of these findings in more diverse ageing and stroke populations.

6.5 Future work

Building upon the findings of this thesis, there are several key avenues for future research that could further explain the mechanisms, optimise the protocols, and expand the clinical application of neural-targeted interventions such as FAT.

First, large-scale clinical trials are warranted to validate the efficacy of FAT in older adult populations with varying degrees of frailty, comorbidities, and baseline neuromuscular impairment. While the current work demonstrates significant neural adaptations over a relatively short training period, determining the scalability, feasibility, and adherence to FAT in real-world community and clinical settings is essential. These trials should include long-term follow-up to assess the persistence of adaptations and their translation into reductions in falls, improvements in mobility, and enhanced independence. That we were able to see improvements in neuromuscular function in just 4-weeks may have relevance in time-limited clinical situations where the window for intervention is short (i.e., in the UK, the mandated maximum time frame between decision to treat and surgery for cancer

is 31 days (NHS, 2025)). However, if greater improvements can be seen with a longer period of intervention warrants further investigation.

Second, the mechanistic underpinnings of both adaptation to FAT and CE in different muscle groups require further exploration. The present thesis compared proximal and distal lower limb muscles in older adults, but additional work is needed to establish whether these findings generalise to upper limb muscles, or to other lower limb muscles with different functional demands (i.e., those involved in postural control) and fibre-type compositions. Recent work has shown that different muscles of the lower limb have differing responses to an unloading stimulus (Kilroe et al., 2019). As such, it is likely that responses to loading (i.e., FAT) will also be different. Advanced neurophysiological tools, including HDsEMG combined with transcranial magnetic stimulation (TMS; (Škarabot et al., 2023, Thorstensen, 2023)) and high-density electroencephalography (EEG; (Delcamp et al., 2024)), could provide more comprehensive insight into cortical and spinal adaptations associated with FAT. For example, a concurrent TMS–EEG study in chronic stroke demonstrated that the ipsilesional M1 shows reduced N100 TEP amplitude and decreased theta-band intra/interhemispheric connectivity, both of which correlated with corticospinal excitability (Bai et al., 2023). In simple terms, these measures provide insight into the efficiency of neural signal transmission from the brain to the muscles. A reduced N100 amplitude is thought to reflect impaired intracortical inhibition, meaning the brain's ability to regulate and fine-tune motor output is compromised, while altered theta connectivity suggests disrupted coordination and communication between motor regions across hemispheres. Such changes likely mean that after stroke, the motor cortex may be less able to modulate and synchronise output to spinal motor neurons, contributing to deficits in voluntary force production and motor control. Similarly, TMS–EEG has provided direct

evidence of interhemispheric imbalance after stroke (Casula et al., 2021), where excessive activity in the contralesional hemisphere can inhibit the damaged hemisphere. This imbalance is relevant to rehabilitation because interventions that restore symmetry in cortical excitability have been linked to improved motor recovery.

Third, there is a need to optimise FAT parameters to maximise neural adaptation. Future studies should systematically investigate the effects of contraction type, target waveform complexity, visual feedback modalities, and training volume on both local and contralateral outcomes. For 'traditional' RET, the long-held belief that high-intensity (i.e., high-load) was the most effective means by which to elicit muscle hypertrophy was challenged by work from Burd et al. (2010) who showed that when each intensity was performed to volitional failure, repetitions at 30% 1-repetition maximum (1-RM) elicited the same increase in muscle protein synthesis (MPS; the metabolic process underpinning muscle hypertrophy) as those performed at 90% 1-RM (Burd et al., 2010). Although the present FAT protocol did not involve training to failure, this study illustrates that low-load contractions can, under certain conditions, stimulate similar anabolic signalling to high-load work, and therefore supports further exploration of low-load paradigms for neural and muscular adaptation. Also, highlighting the importance of optimising training parameters, Lipski et al. (2025) has recently shown that with no alterations in session number or duration, eccentric compared to concentric high-intensity interval training (HIIT) elicits superior improvements in power and muscle size (RET) (Lipski et al., 2025). Furthermore, the interaction between FAT and other interventions, such as RET, balance training, or neuromodulation (e.g., transcranial direct current stimulation), may reveal synergistic effects that enhance both neural and muscle function (Reis et al., 2009, Lattari et al., 2020).

Fourth, the translation of FAT into stroke rehabilitation deserves focused investigation. The bilateral impairments in stroke survivors documented herein support the rationale for integrating FAT into stroke rehabilitation programmes based on our evidence of CE, and therefore the potential for this form of intervention to improve function in both the paretic and non-paretic limb. Although there are studies exploring cross-education effects of resistance or skill-based training in stroke survivors, with reported contralateral strength gains of ~8–25% and improvements in functional tasks such as sit-to-stand and gait speed (Manca et al., 2018, Hendy and Lamon, 2017, Smyth et al., 2023a), to our knowledge, while motor control and skill-based interventions have been examined in stroke rehabilitation, no study has specifically explored the potential of a FAT intervention in this population. Future randomised controlled trials (RCTs) should examine whether unilateral FAT in the non-paretic limb can produce meaningful improvements in paretic limb function, reduce asymmetry, and accelerate functional recovery.

In current practice, stroke rehabilitation typically begins as soon as the patient is medically stable, often within the first 24–72 hours post-event in acute-care settings, progressing to structured task-specific and physiotherapy-based training within 2–6 weeks (Bernhardt et al., 2023, Kwakkel et al., 2020, Kernan et al., 2021). Early rehabilitation is associated with improved functional recovery and reduced long-term disability, provided the intensity is carefully titrated to the patient's tolerance (Alt Murphy et al., 2025, Langhorne et al., 2020). Although the present thesis focused on chronic stroke survivors, these guidelines emphasise the potential benefit of integrating neural-targeted approaches such as FAT earlier in the rehabilitation continuum. Although the work of Saunders et al. (2020) explored the impact of commencing stroke rehabilitation at 2 weeks versus 6 months, they employed

conventional RET, and as such, these findings may not be directly transferable to FAT (Saunders et al., 2020).

Finally, biomarker development may enhance the precision and personalisation of neural-targeted interventions. Baseline measures of MUDR variability, recruitment patterns, and corticospinal excitability could help predict individual responsiveness to FAT or CE potential, enabling tailored pre-/rehabilitation strategies that maximise benefit while minimising unnecessary effort/cost. However, the development of a biomarker for exercise responsiveness is not an easy challenge, and not one that has been met to date. Despite ~20% of individuals not achieving a numerical improvement in the expected primary endpoint of RET (i.e., hypertrophy (Mann et al., 2013)), endurance exercise training (cardiorespiratory fitness (CRF) or insulin sensitivity (Álvarez et al., 2017)), or HIIT (CRF (Bonafiglia et al., 2016)), this is not linked to baseline characteristics (e.g., age, sex, muscle mass) or baseline ability in the aforementioned endpoints (Meyler et al., 2021). To date, no biomarker for responder status to exercise exists.

In conclusion, the findings of this thesis provide a strong foundation for the continued development of low-load, neural-targeted exercise interventions. Future work should focus on scaling up, refining protocols, and integrating these approaches into multidisciplinary rehabilitation frameworks. With further validation, FAT (and its ability to elicit CE) have the potential to become an integral component of evidence-based strategies aimed at preserving and restoring neuromuscular function in ageing and clinical populations.

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Appendix

8.1 Appendix I:

Systematic Review and Meta-analysis PROSPERO Protocol

ID: CRD42023458818

Review title

Impact of Cross-Education on the Lower Limb Muscle Strength Following Resistance Training in Healthy Population: A Systematic Review and Meta-Analysis

Original language title

N/A

Review question

What is the impact of cross-education following Resistance Training techniques on the strength of untrained lower limbs among healthy participants?
What range of strength increase can be expected in the untrained lower limb as a result of cross-education among healthy participants?
Does the existing literature support a consistent and quantifiable link between cross-education and strength improvement in untrained lower limbs among healthy participants?

Searches

We will conduct our search in the following databases: MEDLINE (via PubMed), the Cochrane Library (CENTRAL), Web of Science (Core Database), SCOPUS, EBSCO-host, and Ovid-Embase. The key search terms we will use include: "cross-education", "cross-transfer", "cross-training", "interlimb transfer", "strength transfer", "contralateral strength training", "unilateral strength training", "Resistance Training", "resistance exercise", "lifting", "weight lifting", "weight training", "strength training", and "power training".
The search will include studies from each database's inception until August 2023.
In terms of restrictions, we will only consider studies that are published and peer-reviewed; grey literature or unpublished studies will not be included in our search.
All searches will be performed in English, but there will be no restrictions on the country of origin of the studies.
Finally, in accordance with good practice, the database searches will be re-run prior to final analysis. Any further eligible studies identified during this final search will be retrieved and included in the systematic review.

URL to search strategy

[Will be provided]

Condition or domain being studied

The domain being studied in this research revolves around strength training and physical fitness, specifically focusing on the phenomenon of cross-education. Cross-education refers to a process where training one limb can lead to strength gains in the contralateral untrained limb. This concept is of significant interest within the fields of rehabilitation, sports science, and general fitness, as it may facilitate better training outcomes and recovery strategies. The primary focus is on the untrained lower limb, and the potential impact cross-education training techniques can have on its strength enhancement. This could have implications for individuals recovering from injury, athletes, or anyone seeking to improve their overall physical strength and conditioning.

Participants/population

For this systematic review and meta-analysis, our study population will include healthy volunteer individuals of all ages, genders, and races who have participated in studies exploring the effects of cross-education on untrained lower limb strength.

Intervention(s), exposure(s).

For this review, the intervention being examined is cross-education strength training. Specifically, this refers to strength training conducted unilaterally, i.e., in one limb, with the intent of improving the strength of the contralateral, untrained lower limb through the effect of cross-education.

Inclusion Criteria:

The intervention must involve unilateral strength training of any form (e.g., resistance training, weight lifting, power training) in one limb.

The study should provide quantitative data on the strength changes in the contralateral, untrained lower limb as a result of the intervention.

Any duration, frequency, and intensity of the unilateral training is acceptable, provided it's explicitly mentioned in the study.

Exclusion Criteria:

Studies where both limbs are simultaneously trained.

Studies where strength training is not the primary intervention.

Any studies with unhealthy participants.

Studies that do not provide explicit and quantifiable outcomes regarding the change in muscle strength in the untrained lower limb.

For the sake of this review, it's important to note that the mode, intensity, frequency, and duration of the training protocols may vary across the included studies. This diversity in intervention parameters is inherent to the field and will be accounted for in the analysis and interpretation of the results.

Comparator(s)/control

In this systematic review and meta-analysis, we will not be focusing on a single comparator or control group due to the diversity of interventions used in the individual studies to be included.

The current literature has a range of control or comparator groups, from bilateral heavy-resistance strength training, unilateral balance training, isokinetic training, various forms of resistance exercise, electro-induced contractions, different velocities and durations of eccentric contractions, to stretching training and maximal strength training. Control groups often involve a non-intervention group, or standard care, or contralateral resistance exercise, amongst others.

Each of these comparators provides unique insights into the effects of cross-education, but none serve as a single, universal comparator. As such, the comparison in our review will be multifaceted, comparing with these varied training techniques or control conditions.

The analysis will take into consideration the diversity of these comparators, and the interpretation of results will be conducted with respect to each individual comparator as reported in the original studies. This will allow for a more comprehensive understanding of the impact of cross-education training on untrained lower limb strength across different exercise protocols and controls.

Types of study to be included

Randomized Controlled Trials

Observational studies, case reports, case series, animal studies, and non-English studies will be excluded.

Context

In this systematic review and meta-analysis, we do not place any specific restrictions on the context or setting of the included studies. We are open to considering studies conducted in various environments, such as hospitals, rehabilitation centers, sports training facilities, research institutions, fitness centers, and home-based training programs.
Additionally, we will not restrict studies based on their geographical location. We aim to include research conducted in any part of the world, including high-income, middle-income, and low-income countries.
In terms of other contextual factors, we do not limit our review based on the participant's level of fitness, experience with strength training, or specific demographic characteristics unless specified in the 'Participants/Population' section.
This broad context inclusion allows us to capture a wide range of studies in the field of cross-education and strength training, thereby enhancing the generalizability and applicability of our review findings.

Main outcome(s).

The main outcome of this systematic review and meta-analysis is the effect of unilateral strength training on the contralateral (untrained) limb's strength. This will be quantitatively assessed by comparing the pre- and post-intervention strength measures in the untrained limb across all included studies. The strength measures may include but are not limited to, maximal voluntary force, peak torque, and muscle work, and these are typically measured using tools such as dynamometers or through performance-based tests.

Additional Outcomes:

Cross-education effects on other aspects of physical performance in the contralateral limb: This includes changes in parameters like balance, range of motion, muscle power, and muscle mass.
Neural adaptations: Changes in neural parameters, such as neural drive or corticospinal excitability, which might explain the observed cross-education effects.
Physiological adaptations: This includes changes in blood lactate levels, oxygen re-perfusion, and other relevant physiological responses.
Comparison of cross-education effects between different forms of training: This includes comparing high-load vs low-load resistance training, eccentric vs concentric training, traditional vs non-traditional set configurations, and others.
Differences in cross-education effects across different demographic groups: This may include differences based on age, gender, or other participant characteristics.
Practical applicability and implications for rehabilitation: Insights into the utility of unilateral strength training for rehabilitation after unilateral injury, for individuals with conditions causing unilateral strength reductions, or in situations where bilateral exercises are not feasible.
Effect of training duration and frequency: Impact of varying lengths and frequencies of training programs on the observed cross-education effects.
These additional outcomes will be analyzed using the specific measures reported in the included studies, such as balance measures, neurophysiological assessments, physiological measures, and others

Study Selection

Two independent reviewers will perform the selection of studies for inclusion in the systematic review based on the eligibility criteria previously defined. This process will be conducted in a blind manner, with each reviewer not being aware of the other's decisions. The selection process will occur in two stages: first, titles and abstracts of retrieved studies will be screened for potential eligibility; second, full-text articles of potentially eligible studies will be assessed for final inclusion. Discrepancies in the inclusion decisions made by the two reviewers at any stage of the process will be resolved through discussion, and if consensus cannot be reached, a third independent reviewer will be consulted.

Data Extraction

Data will be extracted from the selected studies by two independent reviewers using a pre-designed data extraction form. The form will capture details such as study characteristics (e.g., authors, year, country), study design and methodology (e.g., type of intervention, frequency and duration of the training, and control group details), participant demographics and baseline characteristics (e.g., age and sex), and outcome measures and results (e.g., measures of strength, balance, neural or physiological adaptations, and others as described in our outcomes section).

Any disagreements in the data extracted by the two reviewers will be resolved through discussion and, if necessary, consultation with a third reviewer. In case of missing data, we will attempt to contact the authors of the respective studies for additional information. The extracted data will be entered into an Excel spreadsheet and cross-checked for accuracy.

Risk of bias (quality) assessment

The risk of bias in the included studies will be assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). The RoB 2 tool is a well-established instrument for the evaluation of the risk of bias in randomized controlled trials, focusing on five specific domains:

Bias arising from the randomization process: This will assess the process used to generate the allocation sequence and conceal the allocation prior to assignment, as well as any deviations from the intended interventions.

Bias due to deviations from intended interventions: This domain will evaluate whether the study participants and investigators adhered to the intervention protocol.

Bias due to missing outcome data: We will examine the amount, nature, and handling of incomplete outcome data.

Bias in the measurement of the outcome: This will review the methods used for assessing and recording the outcomes, with an emphasis on blinding of outcome assessment.

Bias in the selection of the reported result: This assesses the possibility of selective outcome reporting.

Each domain will be assessed independently and will be classified as having a 'low', 'high', or 'some concerns' risk of bias according to the guidelines provided by the RoB 2 tool.

The risk of bias assessment will be performed independently by two reviewers, and disagreements will be resolved through discussion and, if necessary, consultation with a third reviewer. Results from the risk of bias assessment will be presented in a 'Risk of bias' summary figure.

Strategy for data synthesis

Quantitative synthesis: For the studies that provide comparable outcomes, we plan to perform a meta-analysis. The Review Manager 5.4 software will be used for this analysis. The choice of a fixed or random effects model will depend on the extent of heterogeneity observed among the studies. If we detect considerable heterogeneity (I^2>50%), a random-effects model will be chosen. Otherwise, we will use a fixed-effect model.
We plan to analyze continuous outcomes using the mean difference (MD) or standardized mean difference (SMD) if different scales are used. For dichotomous outcomes, we will use the risk ratio (RR). All results will be presented with 95% confidence intervals (CI).
Heterogeneity: We will assess statistical heterogeneity using the Chi² test and the I^2 statistic. If there is substantial heterogeneity, we will explore potential sources using subgroup analyses.
Sensitivity Analysis: We will perform sensitivity analyses to evaluate the robustness of the review conclusions, examining the impact of excluding studies with a high risk of bias.
Publication Bias: We will use the Jamovi software to investigate potential publication bias if ten or more studies are included in an outcome. This will be visualized using funnel plots.
The synthesis strategy thus aims to provide a comprehensive analysis of the data obtained from the studies, adhering to the PRISMA guidelines for systematic reviews and meta-analyses.

Analysis of subgroups or subsets

Subgroup Analysis: If there are sufficient data, we will conduct subgroup analyses based on the type of intervention, target population characteristics, and outcome measures.

Type and method of review.

Meta-analysis

Health area of the review

Rehabilitation and Physiotherapy

Language

English

Country

England

Other registration details

N/A

Keywords

Cross-education; Unilateral training; Contralateral training; Resistance Training; Meta-analysis; Lower Limb

Details of any existing review of the same topic by the same authors

N/A

The PICOs of this systematic review and meta-analysis can be summarized as follows:
Population (P): Healthy volunteer individuals of all ages, genders, and races.
Intervention (I): Unilateral strength training of any form, including resistance training, weight lifting, power training conducted in one limb, with the intent of improving the strength of the contralateral, untrained lower limb through the effect of cross-education.
Comparison (C): Various forms of control groups from bilateral heavy-resistance strength training, unilateral balance training, isokinetic training, various forms of resistance exercise, electro-induced contractions, different velocities and durations of eccentric

contractions, to stretching training and maximal strength training. Control groups also often involve a non-intervention group, or standard care, or contralateral resistance exercise, among others.
Outcome (O): The effect of unilateral strength training on the contralateral (untrained) limb's strength. This will be quantitatively assessed by comparing the pre- and post-intervention strength measures in the untrained limb across all included studies. The strength measures may include but are not limited to, maximal voluntary contraction, peak torque, and muscle work.
Study Design: Randomized Controlled Trials
This systematic review and meta-analysis aim to understand the impact of cross-education following resistance training techniques on the strength of untrained lower limbs in a healthy population.

MEDLINE via PubMed <from inception to September 22, 2023>

#1	“cross-education”	202
#2	“cross-transfer”	111
#3	“cross-training”	546
#4	“interlimb transfer”	91
#5	“strength transfer”	22
#6	“contralateral strength training”	9
#7	"unilateral strength training"	57
#8	OR/1-7	945
#9	"Resistance Training"	18,164
#10	"resistance exercise"	7,341
#11	lifting	19,878
#12	"weight lifting"	5,688
#13	"weight training"	1,188
#14	"strength training"	6,874
#15	"power training"	595
#16	OR/9-15	48,495
#7	#8 AND #16	209

Cochrane Library (CENTRAL) <from inception to September 22, 2023>

#1	MeSH descriptor: [Resistance Training] explode all trees	5513
#2	(cross-education):ti,ab,kw	109
#3	(cross-transfer):ti,ab,kw	33
#4	(cross-training):ti,ab,kw	72
#5	(interlimb transfer):ti,ab,kw	22
#6	(strength transfer):ti,ab,kw	22
#7	(contralateral strength training):ti,ab,kw	192
#8	(unilateral strength training):ti,ab,kw	724
#9	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	1435
#10	#1 AND #9	232

Web of Science (Core Database) <from inception to September 22, 2023>

#1	TS=“cross-education”	355
#2	TS= “cross-transfer”	205
#3	TS= “cross-training”	1109
#4	TS= “interlimb transfer”	256
#5	TS= “strength transfer”	65
#6	TS= “contralateral strength training”	10
#7	TS="unilateral strength training"	65
#8	OR/1-7	1923
#9	TS="Resistance Training"	15,821
#10	TS="resistance exercise"	15,938
#11	TS=lifting	116,504
#12	TS="weight lifting"	1,593
#13	TS="weight training"	2,289
#14	TS="strength training"	9,676
#15	TS="power training"	2,728
#16	OR/9-15	153,244
#7	#8 AND #16	287

SCOPUS <from inception to September 22, 2023>

#1	TITLE-ABS-KEY ("cross-education")	267
#2	TITLE-ABS-KEY (“cross-transfer”)	213
#3	TITLE-ABS-KEY (“cross-training”)	1450
#4	TITLE-ABS-KEY (“interlimb transfer”)	102
#5	TITLE-ABS-KEY (“strength transfer”)	76
#6	TITLE-ABS-KEY (“contralateral strength training”)	8
#7	TITLE-ABS-KEY ("unilateral strength training")	61
#8	OR/1-7	2,058
#9	TITLE-ABS-KEY ("Resistance Training")	29,712
#10	TITLE-ABS-KEY ("resistance exercise")	9,997
#11	TITLE-ABS-KEY (lifting)	67,909
#12	TITLE-ABS-KEY ("weight lifting")	8,059
#13	TITLE-ABS-KEY ("weight training")	2,839
#14	TITLE-ABS-KEY ("strength training")	10,403
#15	TITLE-ABS-KEY ("power training")	1,009
#16	OR/9-15	105,264

#7	#8 AND #16	264

Ovid- Embase <from inception to September 22, 2023>

#1	cross-education.mp.	229
#2	cross-transfer.mp.	122
#3	cross-training.mp.	778
#4	interlimb transfer.mp.	99
#5	strength transfer.mp.	30
#6	contralateral strength training.mp.	8
#7	unilateral strength training.mp.	66
#8	1 or 2 or 3 or 4 or 5 or 6 or 7	1215
#9	Resistance Training.mp.	30502
#10	resistance exercise.mp.	8830
#11	lifting.mp.	22039
#12	weight lifting.mp.	6324
#13	weight training.mp.	1936
#14	strength training.mp.	9015
#15	power training.mp.	722
#16	9 or 10 or 11 or 12 or 13 or 14 or 15	57225
#17	8 and 16	250

EBSCOHost CINAHL <from inception to September 22, 2023>

#1	“cross-education”	88
#2	“cross-transfer”	20
#3	“cross-training”	885
#4	“interlimb transfer”	19
#5	“strength transfer”	11
#6	“contralateral strength training”	6
#7	"unilateral strength training"	29
#8	OR/1-7	1,029
#9	"Resistance Training"	9698
#10	"resistance exercise"	7,645
#11	lifting	10,006
#12	"weight lifting"	8,026
#13	"weight training"	7,101
#14	"strength training"	8,007
#15	"power training"	288
#16	OR/9-15	23,707
#17	#8 AND #16	109

8.2 Appendix II

FMHS RESEARCH ETHICS COMMITTEE (FMHSREC)
Ethics Application Form/Protocol
Intervention/ Basic Science/Physiology Studies in Healthy Volunteers

ONLY FULLY SIGNED (electronic) TYPE-WRITTEN APPLICATIONS WILL BE ACCEPTED, BY EMAIL

Please complete this form if your study involves the administration of a licensed drug, herbal remedy, food supplement or physiological intervention/ testing in healthy volunteers AND is NOT a clinical trial.

Should you require any assistance in completing this document, please contact the REC administrator in the first instance: FMHS-ResearchEthics@nottingham.ac.uk

STUDY DETAILS	
Full study title	Low-intensity motor control training (MCT) to manipulate functional outcomes in healthy older adults.
Short title	LI_MCT
FMHS UREC reference	**FMHS 390-1121**
Date and version number	Version 2 – 12/01/2022
Principal investigator	Dr Mathew Piasecki Assistant Professor of Clinical, Metabolic & Molecular Physiology Centre Of Metabolism, Ageing & Physiology (COMAP) Academic Unit of Injury, Inflammation & Recovery Sciences School of Medicine, Faculty of Medicine & Health Sciences
University email contact	Mathew.piasecki@nottingham.ac.uk
Student (if applicable)	Mrs. Nishadi Gamage- PhD in Medicine Mr. Abdulmajeed Altheyab- PhD in Medicine
University email contact	Nishadi.Gamage@nottingham.ac.uk Abdulmajeed.altheyab@nottigham.ac.uk
University telephone contact	01332 724688
Medically qualified collaborator (licensed doctor)	One of the Clinical Research Fellows (all UoN registered PhD students) associated with our research group (Centre of Metabolism, Ageing & Physiology, COMAP) will sign off on participant screening.
Sponsor	The University of Nottingham
External funding	None
Will you submit or have you submitted this study to another ethics committee?	Yes ☐ No ☒

If other relevant approvals for this research are required (e.g. from other universities' ethics committees) please attach them and give more details below:	
Declaration of any conflicts of interest	None
Confidentiality statement	This document contains confidential information that must not be disclosed to anyone other than the authorised individuals from the University of Nottingham, the Investigator Team and members of the Faculty of Medicine & Health Sciences University Research Ethics Committee (FMHS UREC), unless authorised to do so.

RESEARCH TEAM	
Principal investigator (PI) title and name	Dr Mathew Piasecki
Department/institute name	University of Nottingham
Role in study	Principal Investigator – Study oversight
Training/qualification in research ethics	NIHR ICH-GCP Online Training Course (Secondary Care)
Co-investigator (Co-I) title and name	Prof Philip Atherton
Department/institute name	University of Nottingham
Role in study	Co-I – Study oversight
Training/qualification in research ethics	NIHR ICH-GCP Online Training Course (Secondary Care)
Co-investigator (Co-I) title and name	Dr Beth Phillips
Department/institute name	University of Nottingham
Role in study	Study oversight
Training/qualification in research ethics	NIHR ICH-GCP Online Training Course (Secondary Care)
Student name	Nishadi Gamage
Department/institute name	University of Nottingham
Role in study	PhD Student- Medicine
Training/qualification in research ethics	NIHR- GCP Online course (Clinical research network coordinating centre)
Student name	Abdulmajeed Altheyab
Department/institute name	University of Nottingham
Role in study	PhD Student- Medicine
Training/qualification in research ethics	NIHR- GCP Online course (Clinical research network coordinating centre)

SYNOPSIS

Please state why this study is not considered a clinical trial	The study will be conducted on healthy volunteers and will specify non-clinical endpoints	
List all sites where this study will be conducted	University of Nottingham, School of Medicine, Royal Derby Hospital Centre, Derby University of Nottingham, School of Medicine, Queen's Medical Centre, Nottingham	
Age range of study participants	Older adults aged between 65-85 years	
Planned sample size and groups	30 healthy male and female subjects aged between 65-85 years).	
Planned study duration	48 months	
Anticipated start date	06/01/2021	
Anticipated end date	30/12/2025	
	Objectives	**Outcome Measures**
Objectives and outcome measures	To evaluate the alterations to motor control and their underpinning neural mechanisms in response to low-intensity motor control training To establish an effective low-intensity motor control training to improve functional outcomes To evaluate bilateral neuromuscular responses after unilateral fatigue	Primary - motor unit plasticity (size, number, complexity, reliability, firing rate, further exploratory markers) Secondary – clinically relevant functional outcomes (balance, gait, motor control)
Name of drug/ substance/ intervention	Low-intensity motor control training	
Purpose of drug/ substance/ intervention use in this study	With increasing age, it is evident that individuals experience frailty; principally due to the age-related decline in skeletal muscle mass and function, 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. Reduced control of muscles (known as motor control) is known to impact fine motor movements and balance which are useful to perform activities of daily living and to maintain independence, which can often be lost with advancing age. Therefore, the purpose of low-intensity motor control training is to focus on lower limb muscles (Specifically vastus lateralis and tibialis anterior) to investigate whether motor control and muscle function can be improved by exercise training.	
Adverse reactions and side effects posing a particular risk with this treatment	Low-intensity motor control training is completely safe to be applied in human research. The pin-type electrode (which will be used to measure intra-muscular electromyography) may provide slight discomfort for some individuals. However, the needle is smaller than those who used for routine	

	blood samples. The procedure will only be performed by individuals trained and experienced in this technique.

ABBREVIATIONS

ADL	Activities of daily living
Co-I	Co-investigator
EMG	Electromyography
FMHS	Faculty of Medicine & Health Sciences
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
MCT	Motor control training
MRC	Medical Research Council
MVC	Maximal isometric voluntary contraction
NMES	Neuromuscular electrical stimulation
PI	Principal Investigator
PIS	Participant Information Sheet
REC	Research Ethics Committee
RM	Repetition maximum
SOP	Standard Operating Procedure
TA	Tibialis Anterior
UoN	University of Nottingham
VL	Vastus Lateralis

BACKGROUND AND RATIONALE

Background:

The human motor unit (MU) consists of a motor neuron, axon, distal axonal terminals, neuromuscular junctions (NMJ) and skeletal muscle fibres. The MU is considered the final component of the neuromuscular system and it has a significant role in muscle force generation with muscle contraction which occurs via the processes of action potential generation and synaptic transmission. Increases in muscle force are partly mediated by the firing rate of MUs (Piasecki *et al.*, 2021).

With increasing age, it is evident that individuals experience frailty; principally due to the age-related decline in skeletal muscle mass and function, 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 (Wilkinson *et al.*, 2018). Previous findings from our lab have established that in addition to the decline in muscle mass and strength during the ageing process, the peripheral motor nervous system also undergoes motor unit remodelling, which is evidenced by a reduction of motor unit number, and an increase of the motor unit size (Piasecki *et al.*, 2018).

Reduced control of muscles (known as motor control) is known to impact fine motor movements and balance which are useful to perform activities of daily living and to maintain independence, which can often be lost with advancing age (Enoka & Duchateau, 2017).

Therefore, the purpose of low-intensity motor control training is to focus on lower limb muscles (vastus lateralis and tibialis anterior) of older adults, to investigate whether motor control and muscle function can be improved by supervised motor control training. More specifically, we will also determine any cross-education effects, whereby training induced benefits to the trained limb are also apparent in the untrained limb. This will be compared acutely, with a short unilateral muscle fatigue task, and longitudinally with the 4-week supervised motor control intervention. Underpinning mechanisms of possible improvements will be assessed via multiple methods of electromyography, applied to determine central and peripheral adaptations to the training intervention.

Aims:

The primary aim of the present study is to investigate the efficacy of low-intensity motor control training on functional outcomes in healthy older adults.

References:

Enoka RM & Duchateau J (2017). Rate coding and the control of muscle force. *Cold Spring Harb Perspect Med*; DOI: 10.1101/cshperspect.a029702.

Piasecki M, Garnés-Camarena O & Stashuk DW (2021). Near-Fiber Electromyography. *Clin Neurophysiol*; DOI: https://doi.org/10.1016/j.clinph.2021.02.008.

Piasecki M, Ireland A, Piasecki J, Stashuk DW, Swiecicka A, Rutter MK, Jones DA & McPhee JS (2018). Failure to expand the motor unit size to compensate for declining motor unit numbers distinguishes sarcopenic from non-sarcopenic older men. *J Physiol* **596,** 1627–1637.

Wilkinson DJ, Piasecki M & Atherton PJ (2018). The age-related loss of skeletal muscle mass and function: Measurement and physiology of muscle fibre atrophy and muscle fibre loss in humans. *Ageing Res Rev* **47,** 123–132. Available at: https://linkinghub.elsevier.com/retrieve/pii/S156816371830134X.

Experimental protocols:

Subjects

This study will be carried out on 30 healthy subjects (15 males and 15 females aged between 65-85 years). Prior to the study, subjects will complete a medical screening (including blood tests (urea and electrolytes (U & E's), liver function tests (LFT's), thyroid function tests (TFT's), coagulation and fasting glucose), an ECG and blood pressure check) and a general health questionnaire. Abnormal screening results will be discussed with the subject and their GP will be informed. All the subjects will be informed the nature and procedure of the experiment, and the possible risks before they obtain the informed consent.

Assessments

The study consists of:
A screening visit to assess the suitability for the study (~45 minutes)
A baseline visit to assess the muscle function and structure including an acute phase unilateral fatigue (~4 hours)
Four-weeks motor control training (3-sessions per week each lasting ~20 min)
Post-motor control training visit where the baseline visit measures will be repeated.
A follow-up visit: 2 weeks after the completion of motor control training (detraining period of 2 weeks) where the baseline visit measures will be repeated.

Screening Visit

Prior to being enrolled onto the study, participants will be invited for a screening visit to assess the suitability for the study. They will be given the opportunity to ask questions about the study and to provide written consent for the participation in the study. Participants will be requested to attend this session fasted from midnight (although they may drink water freely). This visit will last approximately 45-mins and will include:
A small blood sample to measure health parameters, including liver and kidney function
A medical history discussion
Measures of the height and weight
An assessment of the heart, including an electrocardiogram (ECG) to monitor heart and blood pressure check
Ultrasound measurements: of both lower legs to evaluate 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).

Baseline Study Day

On the first study day, participants will be advised to attend the laboratory fasted at approximately 9am.

Subjects will be studied using the following techniques:
An isometric dynamometer will be used to measure the maximal isometric contraction force (MVC) for lower leg muscles (knee extension and dorsiflexion movements).
Intramuscular electromyography (iEMG) and high-density surface EMG (HD-sEMG) will be used to determine motor unit structure (size & number) and function (firing rate, firing complexity, neuromuscular junction transmission reliability); Surface electromyography to determine muscle activation patterns and the largest compound muscle action potential (M-wave). This will be performed using electrodes and a small pin-type electrode inserted into the thigh (vastus lateralis) and lower leg (tibialis anterior) muscles. Subsequently, participants will be advised to follow force trace line on a monitor during the knee extension and dorsiflexion movements.
Acute phase unilateral fatigue which includes repeated unilateral leg extension using the leg extension machine. Participants will be required to perform 4 sets of 8-12 repetitions on a leg extension machine, at approximately 75% of their 1 rep maximum. The Borg scale will be used to determine the level of perceived fatigue of the participant.
Functional assessments of short physical performance battery (SPPB) tests, balance and fine motor control. Balance tests will include static bilateral stance, single leg stance with eyes open, single leg stance with eyes-closed, timed-up and go (TUG) test and gait analysis.

Training Sessions
The 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 participants will be asked to follow a force trace line, through contraction of the leg muscles, on the monitor in front of them which would vary in intensity throughout each session. The training protocol is described below.

Training protocol

Each participant will complete a three times per week, four-week training program, consisting of standard motor control training (MCT) on bilateral vastus lateralis (VL) and tibialis anterior (TA) muscles.

Participants will complete 2 contractions for each muscle group at 10%, 25% and 40% maximal voluntary contraction (determined in pre-training assessment visit) in a randomised order. The number of oscillations (either 6, 8 or 10) and amplitude (either ±2%, ±4% or ±8%) of the sinusoidal waves will be different to that will be used in experimental testing. Contractions will last 20-30 seconds dependent on contraction intensity and will be separated by 60 seconds' rest.

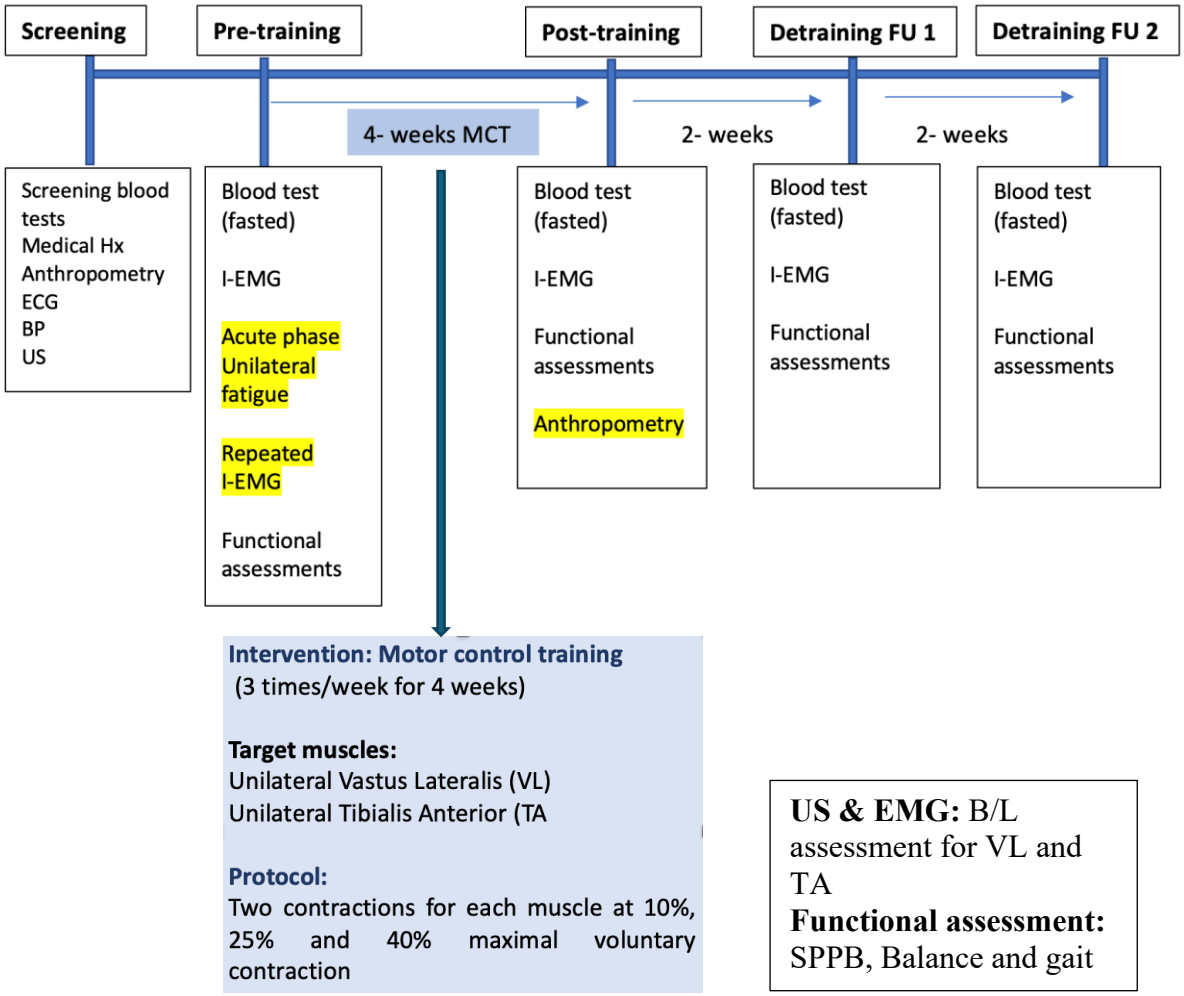


Figure 1: Training protocol
MCT: Motor control training; ECG: Electrocardiogram; BP: Blood pressure; US: Ultrasound scanning; I-EMG: electromyography; B/L: Bilateral; VL: Vastus Lateralis muscle; TA: Tibialis Anterior muscle; SPPB: Short Physical Performance Battery tests.

Post-training Reassessment Study Day
After the motor control training period, participants will be asked to return for another visit where the baseline study day assessments and anthropometric measurements will be repeated.
Two-week detraining follow-up
Two weeks after the completion of the motor control training (detraining), participants will be asked to return for another visit where the baseline study day assessments will be repeated.
Four-week detraining follow-up

Four weeks after the completion of the motor control training (detraining), participants will be asked to return for another visit where the baseline study day assessments will be repeated.

Measurable end points/ statistical power of study
The endpoint of this study is the assessment of motor control and underpinning neural mechanisms in response to training, by detecting the change in motor unit parameters (size, number, complexity, reliability, firing rate, further exploratory markers).

Based on our previous studies in young participants, a power calculation indicates that to detect any improvements in motor control with α of 0.05, β of 0.85, we require 11 participants in each sex group. In view of possible dropouts, we aim to recruit 30 participants consisting of 15 male and 15 females. Sex comparisons are not the primary endpoint of this study; however, they will form exploratory analyses.

Risk summary:
This is a low risk study. Needle insertion for blood tests may cause some bruising although this is rare with good practice and use of the pin electrode for iEMG in some cases can feel uncomfortable, although again this is rare.

PARTICIPANTS

Description of study participants
30 healthy older adults aged between 65-85 years will be recruited in our study, including 15 males and 15 females
Inclusion criteria
Participant is willing and able to give informed consent for participation in the study Healthy volunteers aged between 65-85 years, who are not under any prescribed medications
Exclusion criteria
Subjects will be excluded if they display evidence of: BMI< 18 or >35kg/m2 Participation in any regular and structured exercise training within the past 6 months Musculoskeletal disorders Respiratory disease: COPD; Asthma; Pulmonary hypertension Neurological disorders: Cerebrovascular disease (cerebral haemorrhage; cerebral ischemic stroke); Intracranial space occupying lesion; Epilepsy Metabolic disease: Hyper and hypo parathyroidism; Untreated hyper and hypothyroidism; Cushing's disease; Type 1 or 2 diabetes

Active cardiovascular problems: Uncontrolled hypertension (BP>160/100mmHg); Recent cardiac event; Heart failure (Class III/IV); Arrhythmia; Angina
Active inflammatory bowel disease
Chronic kidney disease
Malignancy (in previous 6 months)
Recent steroid treatment within 6 months or hormone replacement therapy
Family history of early (<55yrs) death from cardiovascular disease

Recruitment

Describe how potential participants will be identified, approached and recruited.

Participants will be recruited by word of mouth, emails to authorised departmental mailing lists and posters located in University departments. We will also put our adverts in the local community and make links with local community groups. Potential participants will complete an expression of interest form and be invited for an initial screening visit to assess eligibility for the study.

Screening and eligibility assessment

Specify the maximum duration allowed between screening and recruitment (if applicable).

Before enrolling on the study, a screening visit will be attended by all participants where a fasted blood sample, medical history, height and weight, electrocardiogram (ECG) and blood pressure will be recorded to confirm suitability for the study. They will also be given the chance to ask questions before giving informed consent. The information obtained from screening will be checked by a clinician to ensure it is safe for the participant to take part. Abnormal screening results will be discussed with the subject and their GP will be informed.

Information provided to participants and informed consent

Specify who will take informed consent, how and when it will be taken.

A written participant information sheet (PIS) (see attached) will be presented to the participants when they express interest in the study. This PIS will detail the exact practical demands of the study, written from the participant's perspective and in simple non-technical language. The participant will be allowed adequate time to consider the information presented in the PIS and will have the opportunity to question the investigative team or other independent parties to decide whether they will participate in the study. After agreeing to participate, written informed consent will require a dated signature by the participant and dated signature of the person who presented and obtained the informed consent (see attached). A copy of the signed informed consent form will be given to the participant. The original signed form will be retained at the study site.

List the names and job roles of the investigative team members who will obtain consent:
Dr Mathew Piasecki, PI
Prof Philip Atherton, Co-I
Dr Beth Phillips, Co-I
Mrs Nishadi Gamage, PhD student
Mr. Abdulmajeed Altheyab, PhD student

Participant confidentiality

Give details about how you will maintain confidentiality of participant's personal and research data.

All study staff will ensure that the participants' data are safeguarded. A single form, for consent for study involvement will carry details of name and address and study ID, 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. Where possible, participants will be identified only by a study ID number on study documents, study samples and on any electronic database containing research data. If participants agree for their contact details to be kept for the purpose of inviting them to take part in future research studies, their name, contact details and date of birth will be stored on a separate database under strict access controls.

STUDY PROCEDURES

Baseline assessments and procedures

Following the screening session where informed consent is given and once eligibility has been confirmed by a clinician assessing blood results and ECG, the participant will attend the first study visit arranged by the research team. One week prior to study, subjects will complete a full assessment of muscle mass, structure and function and establish the interventional intensities.

Muscle structure

The amount of the useful contractile material contained within the muscle (muscle thickness and cross-sectional area (CSA), the architecture of the vastus lateralis (fascicle length and pennation angle) will be assessed by ultrasound.

Blood tests

Medical screening blood tests will be performed prior to study enrolment.
A validated liquid chromatography-mass spectrometry system, ELISA and Multiplex Luminous assays will be used to obtain and analyse the concentrations of circulating hormones and associated biomarkers from pre, post, and follow up visits.

Acute phase- Unilateral fatigue

Acute phase unilateral fatigue which includes repeated unilateral leg extension using the leg extension machine.
Participants will be required to perform 4 sets of 8-12 repetitions on a leg extension machine, at approximately 75% of their 1 rep maximum. The Borg scale will be used to determine the level of perceived fatigue of the participant.

Neuromuscular function

Subjects will be studied using the following techniques:
An isometric dynamometer will be used to measure the maximal isometric contraction force (MVC) and the one-repetition maximum (RM) for lower leg muscles (particularly for knee extension and dorsiflexion movements).
Intramuscular electromyography (iEMG) and high-density surface EMG (HD-sEMG) will be used to determine motor unit structure (size & number) and function (firing rate, firing complexity, neuromuscular junction transmission reliability); Surface electromyography to determine muscle activation patterns and the largest compound muscle action potential (M-wave). This will be performed using electrodes and a small pin-type electrode inserted into the thigh (vastus lateralis) and lower leg (tibialis anterior) muscles. Subsequently, participants will be advised to follow force trace line on a monitor during the knee extension and dorsiflexion movements.
Functional assessments including short physical performance battery (SPPB), balance and fine motor control. Balance tests will include static bilateral stance, single leg stance with eyes open, single leg stance with eyes-closed, timed-up and go (TUG) test and gait analysis.

Subsequent visits

Training Sessions:
Each subject will complete a three times per week, four-week supervised training program. Each training session will last approximately 20-minutes.
During these training sessions participants will be asked to follow a force trace line, through contraction of the leg muscles, on the monitor in front of them which would vary in intensity throughout each session.
Post-training Reassessment Study Day
After the motor control training period, participants will be asked to return for another visit where the baseline study day assessments and anthropometric measurements will be repeated.
Two-week detraining follow-up
Two weeks after the completion of the motor control training (detraining), participants will be asked to return for another visit where the baseline study day assessments will be repeated.
Four-week detraining follow-up
Four weeks after the completion of the motor control training (detraining), participants will be asked to return for another visit where the baseline study day assessments will be repeated.
Finally, the participants will be asked to complete two brief questionnaires about their thoughts on the training programme and the study they have completed.

Sample handling

Blood samples:
10 ml at screening visit and three more blood samples (up to 10 ml) will be taken at baseline visit, end-of-training visit and detraining follow-up visits.

Screening blood samples will be processed by the Royal Derby Hospital pathology lab for normal clinical chemistry assessment and will be disposed of under normal hospital procedures. A validated liquid chromatography-mass spectrometry system, ELISA and Multiplex Luminous assays will be used to obtain and analyse the concentrations of circulating hormones and associated biomarkers from study samples.

Discontinuation/ withdrawal of participants from study

Outline why the study may be discontinued and/or why participants may be withdrawn from the study.

Each participant has the right to withdraw from the study at any time without giving reason. In addition, the research team may discontinue a participant from the study at any time they consider it necessary for any reason including:
Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
Withdrawal of Consent
Non participation in 4 consecutive training sessions

Exclusion of the data for a participant that has withdrawn from analysis will depend on how much data has already been collected and included in analysis at that stage but will be excluded if insufficient.

Withdrawn participants will be replaced to ensure study numbers are achieved. The reason for any withdrawals will be recorded in the study trial master file (TMF).

If a participant is withdrawn due to an adverse event, specify any procedures and/or observations that will continue until resolution of the event. Why will this be necessary?

If an incidental finding of a previously undiagnosed medical or psychiatric condition is discovered unintentionally during the course of the study or at screening (causing withdrawal or not), a clinician will contact the participant and inform their GP. Any adverse events occurring as a result of study practices will be followed up with a clinical member of the research team until resolution, documented in the study TMF, and if serious reported to the ethics committee.

Definition of end of study

Define the end of study for participant involvement.

The end of the study will be the final testing visit (follow up at 4-weeks detraining) for the final participant.

Expenses and benefits

Please detail all expenses or gifts (vouchers, certificates etc.) that will be afforded to participants for taking part and how this will be affected if they do not complete the study.

Every subject who completes the whole study will received £100 inconvenience allowance and they will be able to have the results of their screening and information about their muscle function with an explanation will be given if requested.

INTERVENTION(S) & DRUG ADMINISTRATION

Drug/ Substance/ Intervention 1

Name of drug/ substance/ intervention to be used	Low-intensity motor control training (MCT)
Formulation and route of administration for study	N/A
Dose and route of administration for study	N/A
Duration of treatment for study	Four weeks
Licence status of this drug/substance	N/A
Usual indication	N/A
Usual dose	N/A
Usual duration of treatment	N/A
Where will drug/ substance be sourced from?	N/A
Where will drug/substance be stored?	N/A
How will drug/substance be dispensed?	N/A
How will the drug/ substance be prepared by the researchers for use in this study?	N/A

SAFETY

Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a substance has been administered, including occurrences which are not necessarily caused by or related to that substance.
Adverse Reaction (AR)	An untoward and unintended response in a participant to a substance, which is related to any dose administered to that participant. A causal relationship between the administered substance and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study intervention qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: results in death is life-threatening requires inpatient hospitalisation or prolongation of existing hospitalisation results in persistent or significant disability/incapacity consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

	NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product set out in its summary of product characteristics (SmPC).

Reporting Procedures for Serious Adverse Events or Reactions

A serious adverse event (SAE) occurring to a participant should be reported to UoN FMHS UREC where, in the opinion of the PI, the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' (the type of event is not listed on this form as an expected occurrence). Reports of related and unexpected SAE's should be submitted by the PI within 7 days of the event. For fatal and life-threatening SUSARs, this will be done no later than 3 calendar days after the Sponsor or PI is first aware of the reaction. Any additional relevant information will be reported within 7 calendar days of the initial report.

Safety of Participants

What level of baseline screening will take place for this study?
Before enrolling, a screening visit will be attended by all participants where a fasted blood sample, medical history, height and weight, electrocardiogram (ECG) and blood pressure will be recorded to confirm suitability for the study. They will also be given the chance to ask questions before giving informed consent. The information obtained from screening will be checked by a clinician to ensure it is safe for the participant to take part.
Provide details about the safety monitoring of participants and the staff/researchers carrying this out
Email will be used to communicate with participants regarding participation in the study and timings of study days, but no further monitoring is required. During the study days the participant will be accompanied by a member of the research team at all times.
Give details on the medical cover required and who will provide this cover
A clinician is required to check the screening results to ensure that the participant is eligible to take part in the study and will also be needed for insertion of the intravenous cannula in the arm for blood collection.
Will the participants' GP be informed about their participation in the study?

This would be regarded as essential if the study includes consumption of drugs or novel chemical entities or if you are recommending that the volunteer should see their GP as a result of the study. No, GP's will only be contacted if there is an incidental finding.
What is your planned procedure if an incidental finding is suspected?
If an incidental finding of a previously undiagnosed medical or psychiatric conditions is discovered unintentionally during the course of the intervention or at screening, a clinician will contact the participant and their GP. At screening phase, subjects will receive blood sample collection, ECG, and medical health questionnaire to assess the health condition, whereas it is unlikely that any abnormalities that may be present during exercise interventions.

Ethical Considerations

Most research carries the risk of some ethical challenge. If this is the case you need to demonstrate your awareness of the problem and your response to mitigate ethical objections. There is a free text box below to detail any study specific ethical issues, however the following areas are often a cause for concern:

Will you include any vulnerable participants (e.g. children, elderly)? **If yes,** please describe how they are defined as vulnerable and detail any approved procedures or guidance that you feel apply.	Yes ☐	No ☒
Will taking part in the research put participants under any particular burden and/ or risk? **If yes,** describe how this will be mitigated.	Yes ☒	No ☐
1. Venepuncture for blood sampling This is a low risk procedure that will be carried out by trained staff. There is a risk of bruising following this procedure, however applying pressure to the puncture site once the sample has been obtained will minimize the risk. **2. Intramuscular electromyography (iEMG) and high-density surface electromyography (HD-sEMG)** Throughout several of the tests we will simultaneously record the electrical activity of the muscle using EMG, which involves inserting a small needle (24 gauge) electrode into the muscle of interest. The needle will be inserted around the belly of the muscle (motor point), once the area has been cleaned with alcohol adhesive wipes. The experimenter will wash hands thoroughly and put on gloves using clean technique. The needle will be unsheathed and inspected to ensure it is structurally intact. The experiment will then insert the needle into the muscle until an appropriate depth is reached (0.5-2.5cm depending on target muscle and muscle size), then slightly retract the needle during brief rest breaks between contractions, to ensure different areas of muscle are sampled from. Once complete, the needle will be withdrawn and immediately be disposed into a sharps bin. This is an established technique and is well tolerated among young and old participants. The experimenter will check the subject is comfortable through verbal questioning and observation of any behavioural changes in colour (pale/ flushed/sweating) or eye movement(dilated/contracted).		

Will the research involve deliberate *<u>deception</u>* of participants? **If yes**, justify why deception is used, describe deception and debriefing process, and include debriefing documents in the application.	Yes ☐	No ☒
Will any procedures affect your own or any member of the research teams physical and/ or psychological safety as a researcher? **If yes,** describe how this will be mitigated.	Yes ☐	No ☒
Does your research raise issues relevant to the Counter-Terrorism and Security Act (the Prevent Duty), which seeks to prevent people from being drawn into terrorism? **If yes,** please say how you plan to address any related risks.	Yes ☐	No ☒
Please give details of any other study-specific ethical and/or safety considerations.		
N/A		

STATISTICS AND ANALYSIS

Do you have a statistical plan? **If no,** please justify.	Yes ☒	No ☐
All data will be presented as mean ± SD unless stated otherwise. Two-factor repeated measures of ANOVA test will be executed to within-group to assess changes in functional outcomes. Multi-level mixed effects linear regression models will be used to assess changes within multiple motor units across individuals and time points. Significance level will be set at $p < 0.05$. Data analysis will be performed using GraphPad Prism Version 8 (GraphPad Software, CA, USA) for analysis involving two-way repeated-measures ANOVA, and STATA SE Version 16 (StataCorp, Texas, USA) for multi-level mixed effects regression.		
Number of participants & group allocations		
30 in total; 15 males and 15 females		
Have you done a sample size calculation? If yes, please give details below. If no, please give details to indicate you have considered the implications the selected sample size will have on the study outcome.	Yes ☒	No ☐
Based on our previous studies in young participants, a power calculation indicates that to detect any improvements in motor control with α of 0.05, β of 0.85, we require 11 participants in each sex group. In view of possible dropouts, we aim to recruit 30 participants consisting of 15 male and 15 females. Sex comparisons are not the primary endpoint of this study however they will form exploratory analyses.		
Analysis of Outcome Measures		
EMG parameters will be analysed using previously established methods (Piasecki et al, 2018) in Spike and DQEMG software. Multilevel mixed-effects models will be applied to populations of MUs from each participant, at each timepoint.		

DATA MANAGEMENT

Who will have access to the *research* data?	For the purpose of analysis, all members of the research team will have access to the anonymised research data. Research data in an anonymised form may be disseminated in the form of a thesis, journal articles and conference presentations.
How will *research* data be stored?	Paper documents will be kept securely within a folder in a locked cabinet within the Derby Medical School in a secure and locked office. Identifiable and anonymised data will be stored separately. Electronic information will be stored anonymised on a password protected computer(s).
How long will *research* data be stored for?	All research data will be kept securely for 7 years.
What will be done with the *research* data at the end of the storage period?	This will be deleted and/or disposed of securely.
Who will have access to the participants' *personal* data?	Access to identifiable (personal) information is restricted to personnel directly involved in the study visits. Access to this data will also be granted to authorised representatives from the University of Nottingham and any host institution for monitoring and/or audit of the study to ensure compliance with regulations.
How will *personal* data be stored?	This will be kept securely in a locked cabinet within the Derby Medical School in a secure and locked office and will be separate to the research data.
How long will *personal* data be stored for?	To comply with the data protection act, personal data will be deleted as soon as possible after it is no longer needed for the study. Contact information will be kept by the University of Nottingham for 5 years separate from the research data in order to get in touch with participants for future studies if they consent to this data use.
Describe method(s) of research data entry/management	All study data will be entered on an Excel spreadsheet or other required software in an anonymised fashion. The participants will be identified as a unique study specific code will be used in all databases. Any documentation with identifiable (personal) data will be stored securely and separate from the research data.

STUDY MONITORING AND OVERSIGHT

Who will be responsible for day-to-day supervision of the study?
Dr Mathew Piasecki
Give information about frequency of meetings that will be held to discuss progress/problems. Who will be present at the meetings?
Monthly or more frequently if necessary. Dr Mathew Piasecki, Dr Beth Philips, Prof Philip Atherton, Nishadi Gamage and Abdulmajeed Altheyab will be present at all meetings.

ETHICAL AND REGULATORY CONSIDERATIONS

Declaration of Helsinki

The PI will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

Approvals

This form, an informed consent form, a participant information sheet(s) and any proposed advertising material will be submitted to the UoN FMHS REC for written approval. The research team will submit and, where necessary, obtain approval from the UoN FMHS REC and any other above-mentioned parties for all amendments to the original approved documents.

End-of-Study Report

The PI shall request, complete and submit an end-of-study report to the UoN FMHS REC within 6 months of the study end (participant involvement).

DISSEMINATION AND FEEDBACK OF STUDY OUTCOMES

Data collected during the study will be published in the scientific literature and presented at conferences. Some of the research may also be written up as a thesis. On successful submission of the thesis, it will be deposited both in print and online in the University archives, to facilitate its use in future research. The thesis will be published open access. The study participants can request information about the outcomes from the study team.

REFERENCES

No further references

DECLARATIONS AND SIGNATURES

I/ we, the researcher(s) agree:

To start this research study only after obtaining approval from the UoN FMHS REC;

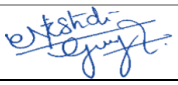
To carry out this research study only if funding is adequate to enable it to be carried out according to good research practice and in an ethical manner;

That it is the responsibility of the PI to ensure that all researchers working on this project are qualified and either experienced, or have received appropriate training (including ethical training), to conduct the research described;

To provide additional information as requested by UoN FMHS REC before approval is secured and as research progresses;

To maintain the confidentiality of all data collected from or about study participants;

To notify UoN FMHS REC in writing immediately of any proposed change which would increase the risk or burden that any participant is exposed to, and await approval before proceeding with the proposed change;
To notify UoN FMHS REC if the PI on the study changes and supply the name of the successor;
To notify UoN FMHS REC in writing within seven days if any serious adverse event occurs in the course of research;
To use data collected only for the study for which approval has been given;
To grant access to data only to authorised persons; and
To maintain security procedures for the protection of personal data, including (but not restricted to): removal of identifying information from data collection forms and computer files, storage of linkage codes in a locked cabinet, and password control for access to identified data on computer files.

Principal Investigator (Name)	Dr Mathew Piasecki
Principal Investigator (Signature)	
Medically qualified collaborator (Name)	N/A
Medically qualified collaborator (Signature)	N/A
Student (Name)	Mrs. Nishadi Gamage
Student (Signature)	
Student (Name)	Mr. Abulmajeed Altheyab
Student (Signature)	

CHECKLIST: (mark as complete (X) or non-applicable (N/A):

Completed form signed by the PI **X**
Medically qualified collaborator indemnity where applicable **N/A**
Data Management Plan **X**
Participant information sheet (PIS) **X**
Informed consent form (ICF) **X**
Poster or advert or draft of text to be used in social media **X**
Letters of permission from gatekeepers, outside institutions where applicable **N/A**

Plan of action in case there is a problem or something of concern is raised where applicable **X**
Drug data sheets and/or information about food/substances being ingested/applied where applicable **N/A**
Standard protocols for procedures i.e. muscle biopsy, blood taking **X**
Safety information for any devices and procedures used where applicable **X**
Participant medical Screening questionnaires **X**
For research being conducted overseas: an outline of the research ethics regulations, local laws and permissions, required **N/A**
Any additional relevant information **N/A**

Applications must be submitted to: FMHS REC Administrator– FMHS-ResearchEthics@nottingham.ac.uk **at least two weeks before the meeting.** This is necessary to ensure that all members of the Committee can adequately review the application. Applications received after this time will be held over until the following meeting. Approval cannot be given to protocols by Chair's action.*

*Except Studies involving blood taking only, where the information generated is of no prognostic significance (i.e. for lab based cell biology studies) These studies will be approved by Chair's action provided no more than a total of 500mls of blood is taken over a 6-month period and no more than 200mls is taken on a single occasion. For these studies applicants need to submit 1 copy of this form and the other required documentation plus a cover letter detailing the nature of the study.

AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

University of Nottingham
UK | CHINA | MALAYSIA

Faculty of Medicine & Health Sciences Research Ethics Committee
Faculty Hub
Room E41, E Floor, Medical School
Queen's Medical Centre Campus
Nottingham University Hospitals
Nottingham, NG7 2UH
Email: FMHS-ResearchEthics@nottingham.ac.uk

16 February 2022

Nishadi Gamage
PhD Student in Medicine
Centre for Metabolism, Ageing & Physiology
Academic Unit of Injury, Inflammation & Recovery Sciences
School of Medicine, University of Nottingham
Royal Derby Hospital Centre
Uttoxeter Road, Derby
DE22 3DT

Dear Mrs Gamage

Ethics Reference No: FMHS 390-1121 – **please always quote**	
Study Title: Low-intensity motor control training (MCT) to manipulate functional outcomes in healthy older adults. (LI-MCT)	
Chief Investigator/Supervisor: Mathew Piasecki, Assistant Professor of Clinical Metabolic & Molecular Physiology, Centre of Metabolism, Ageing & Physiology (COMAP), Academic Unit of Injury, Inflammation & Recovery Sciences (II&RS), School of Medicine.	
Lead Investigators/student: Nishadi Gamage PhD Student, Abdulmajeed Altheyab, PhD Student, COMAP, II&RS, School of Medicine	
Other Key investigators: Philip Atherton, Professor of Clinical, Metabolic & Molecular Physiology, Beth Phillips, Professor of Professor of Translational Physiology, COMAP, II&RS, School of Medicine.	
Proposed Start Date: 06/01/2021	**Proposed End Date:** 30/12/2025

Thank you for responding to the comments made by the Committee at its meeting on 12 November 2021 and the following documents were received:

- FMHS REC Application form and supporting documents version 2.0: 12/01/2022

These have been reviewed and are satisfactory and the research study is given a favourable ethics opinion.

A favourable ethics opinion is given on the understanding that:

1. The protocol agreed is followed and the Committee is informed of any changes using a notice of amendment form (please request a form).
2. The Chair is informed of any serious or unexpected event.
3. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely



Dr VG Wilson, Associate Professor and Reader in Autonomic Pharmacology
Division of Physiology, Pharmacology and Neuroscience, School of Life Sciences
Acting Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

8.3 Appendix III

FMHS RESEARCH ETHICS COMMITTEE (FMHSREC)
Ethics Application Form/Protocol
Intervention/ Basic Science/Physiology Studies in Healthy Volunteers

ONLY FULLY SIGNED (electronic) TYPE-WRITTEN APPLICATIONS WILL BE ACCEPTED, BY EMAIL

Please complete this form if your study involves the administration of a licensed drug, herbal remedy, food supplement or physiological intervention/ testing in healthy volunteers AND is NOT a clinical trial.

Should you require any assistance in completing this document, please contact the REC administrator in the first instance: FMHS-ResearchEthics@nottingham.ac.uk

STUDY DETAILS	
Full study title	CHARACTERISING THE NEUROMUSCULAR FUNCTION OF STROKE PATIENTS DURING RECOVERY
Short title	cSTROKE
FMHS REC reference	FMHS 188-0524
Date and version number	11/03/2024 version 1.0
Principal investigator	Professor Bethan Phillips Centre Of Metabolism, Ageing & Physiology (COMAP) Academic Unit of Injury, Recovery & Inflammation Sciences (IRIS) School of Medicine, Faculty of Medicine & Health Sciences
University email contact	beth.phillips@nottingham.ac.uk
Co-investigator	Dr Mathew Piasecki Centre Of Metabolism, Ageing & Physiology (COMAP) Academic Unit of Injury, Recovery & Inflammation Sciences (IRIS) School of Medicine, Faculty of Medicine & Health Sciences
University email contact	mathew.piasecki@nottingham.ac.uk
Student (if applicable)	Mr Abdulmajeed Altheyab - PhD in Medicine
University email contact	Abdulmajeed.altheyab@nottigham.ac.uk
University telephone contact	01332 724688
Medically qualified collaborator (licensed doctor)	Professor Timothy England, Professor of Stroke Medicine Academic Unit of Translational Medical Sciences (TMS) School of Medicine, Faculty of Medicine & Health Sciences
Sponsor	The University of Nottingham
External funding	None

Will you submit or have you submitted this study to another ethics committee?	Yes ☐	No ☒
If other relevant approvals for this research are required (e.g., from other universities' ethics committees) please attach them and give more details below:		

Declaration of any conflicts of interest	None
Confidentiality statement	This document contains confidential information that must not be disclos to anyone other than the authorised individuals from the University of Nottingham, the Investigator Team and members of the Faculty of Medicine & Health Sciences University Research Ethics Committee (FMHS REC), unless authorised to do so.

RESEARCH TEAM	
Principal investigator (PI) title and name, job title	Professor Bethan Phillips, Professor of Translational Physiology
Department/institute name	University of Nottingham Centre Of Metabolism, Ageing & Physiology (COMAP) Academic Unit of Injury, Recovery & Inflammation Sciences (IRIS) School of Medicine, Faculty of Medicine & Health Sciences
Role in study	Principal Investigator – Overall study oversight
Training/qualification in research ethics	NIHR ICH-GCP Online Training Course (Secondary Care) FMHS REC Member/Deputy Chair >10y
Research Integrity Training	Yes
UoN Code of Research Conduct and Research Ethics	Yes
Co-investigator (Co-I) title and name	Dr Mathew Piasecki, Associate Professor of Neuromuscular Physiology
Department/institute name	University of Nottingham Centre Of Metabolism, Ageing & Physiology (COMAP) Academic Unit of Injury, Recovery & Inflammation Sciences (IRIS) School of Medicine, Faculty of Medicine & Health Sciences
Role in study	Co-investigator – Neuromuscular methods oversight
Training/qualification in research ethics	NIHR ICH-GCP Online Training Course (Secondary Care) UNMSD REC Member
Research Integrity Training	Yes

UoN Code of Research Conduct and Research Ethics	Yes
Co-investigator (Co-I) title and name	Professor Timothy England, Professor of Stroke Medicine
Department/institute name	Professor Timothy England, Professor of Stroke Medicine Academic Unit of Translational Medical Sciences (TMS) School of Medicine, Faculty of Medicine & Health Sciences
Role in study	Co-principal Investigator – Overall study oversight
Training/qualification in research ethics	NIHR ICH-GCP Online Training Course (Secondary Care)
Research Integrity Training	Yes
UoN Code of Research Conduct and Research Ethics	Yes
Student name	Abdulmajeed Altheyab, PhD Student (Medicine)
Department/institute name	University of Nottingham Centre Of Metabolism, Ageing & Physiology (COMAP) Academic Unit of Injury, Recovery & Inflammation Sciences (IRIS) School of Medicine, Faculty of Medicine & Health Sciences
Role in study	Day-to-day study oversight
Training/qualification in research ethics	NIHR-GCP Online course (Clinical Research Network Coordinating Centre)
Research Integrity Training	Yes
UoN Code of Research Conduct and Research Ethics	Yes

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SYNOPSIS

Please state why this study is not considered a clinical trial	The study will be conducted on volunteers with a history of stroke recruit from the community and will specify non-clinical (physiology) endpoints	
List all sites where this study will be conducted	University of Nottingham Medical School at Derby (UNMSD), Royal Derby Hospital.	
Age range of study participants	Adults over 18 years old	
Planned sample size and groups	16 participants all of whom have suffered a stroke in the last 5 years and self-report as having persisting deficits affecting a limb/s on one side.	
Planned study duration	24 months	
Anticipated start date	01/05/2024	
Anticipated end date	01/05/2026	
	Objectives	**Outcome Measures**
Objectives and outcome measures	To determine the impact of stroke on neuro/muscular aspects beyond the point of spontaneous recovery, specifically: Central and peripheral components of neuromuscular function of the affected and non-affected limbs. Strength and physical function (balance, gait etc.) of the affected and non-affected limbs.	Primary: Motor unit features via electromyography (EMG) – Size Number Complexity Reliability Firing rate Secondary: Clinically relevant functional outcome – Motor control Strength Dexterity Balance Gait Overall physical function
Name of drug/ substance/ intervention	No intervention will be applied, this study will compare the neuromuscul characteristics of stroke survivors with age-matched control participants (data already collected as part of a previous study).	
Purpose of drug/ substance/ intervention use in this study	N/A	
Adverse reactions and side effects posing a particular risk with this treatment	N/A	

ABBREVIATIONS

ADL	Activities of daily living
BP	Blood Pressure
CVA	Cerebrovascular Accidents
DALYs	Disability-Adjusted Life-Years
DOMS	Delayed Onset Muscle Soreness
ECG	Electrocardiogram
FAT	Force Accuracy Training
FMHS	Faculty of Medicine & Health Sciences
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
iEMG	Intramuscular Electromyography
MU	Motor Unit
MVC	Maximum Voluntary Contraction
NICE	National Institute for Health and Care Excellence
PI	Principal Investigator
PIS	Participant Information Sheet
REC	Research Ethics Committee
RM	Repetition maximum
SOP	Standard Operating Procedure
sEMG	Surface Electromyography
UoN	University of Nottingham

BACKGROUND AND RATIONALE

In developed countries, strokes are the third most common cause of death and disability (Pollock et al., 2014). Stroke is defined by the World Health Organization (WHO) as "rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin"(Aho et al., 1980). In 2013, the American Heart Association added the term "silent pathology" to the definition, which includes silent haemorrhage and infarctions of the brain, spinal cord, and retina (Sacco et al., 2013). A transient ischemic attack (TIA) is considered a "warning stroke" because although it has similar symptoms to a stroke, the symptoms last for less than 24 hours. Furthermore, approximately 50% of strokes happen within 24 hours of a TIA (Coupland et al., 2017).

The National Institute for Health and Care Excellence (NICE) estimates that in the UK a stroke occurs once every five minutes, and 100,000 people suffer from strokes annually. Further, over 1.3 million individuals in the UK have survived a stroke, with two-thirds of these survivors leaving the hospital with some physical impairment (Linden, 2020). There are 32,000 stroke-related fatalities annually in England alone (Marshall et al., 2022), and stroke results in an annual expenditure in the region of £26-billion across the UK (Linden, 2020). In the previous 15 years, there has been a 49% decrease in the number of deaths caused by stroke in the UK (Marshall et al., 2022) despite an ageing population and that advancing age is a clear risk factor for stroke (Yousufuddin and Young, 2019). This is likely due to advancements in both clinical treatment pathways and public awareness.

Despite this reduction in deaths, in terms of disability-adjusted life-years lost (DALY's), stroke is still the second-highest leading cause of death and is considered to be the third-leading cause of disability globally (Feigin et al., 2022). In 2020, one in six cardiovascular disease-related deaths were caused by strokes. Global costs associated with stroke are projected to exceed 721 billion dollars (0.66 % of the global GDP). The burden (in terms of the absolute number of cases) grew dramatically from 1990 to 2019, with the bulk of worldwide stroke burden lying in lower and lower to middle-income countries (86.0% of fatalities and 89.0% of DALY's). This rise may be linked to a 70 % increase in incident of strokes, a 44 % increase in stroke-related mortality, a 102 % increase in general strokes, and a 143 % increase in prevalent strokes (Feigin et al., 2022). Therefore, stroke is a disease of immense importance to the global population's health, with significant repercussions for individuals, the economy and society. In the past, it was believed that stroke primarily impacted wealthy nations. In contrast, the burden of stroke has fallen dramatically in many developed countries due to the use of evidence-based management techniques (Grefkes and Fink, 2020).

One hallmark of stroke is its tendency to cause unilateral deficits, affecting one side of the body. This can lead to weakness, paralysis, and sensory disturbances. These deficits pose significant challenges for daily activities and can have profound psychological and social impacts. Addressing these unique features is vital in rehabilitation, where tailored interventions can improve outcomes and quality of life for stroke survivors. Some of the current stroke rehabilitation strategies include Constraint-Induced Movement Therapy (CIMT), Task-Specific Training, Functional Electrical Stimulation (FES), Robot-Assisted

Therapy, Virtual Reality (VR) Rehab, and Cognitive Rehabilitation. These approaches all aim to maximize recovery and improve functional outcomes post-stroke (Dobkin, 2005).

As the number of stroke survivors grows due to demographic shifts in our ageing societies, novel strategies for neurorehabilitation are required. Neural reorganisation is the most important driver of functional recovery after a stroke. An enhanced knowledge of the mechanisms that enable plasticity and recovery is required for the development of novel, neurobiologically informed techniques to promote functional recovery (Grefkes and Fink, 2020).

In sum, a better understanding of the neuromuscular deficits caused by stroke, which will be gained from this pilot study, will allow enhanced future design of rehabilitation interventions, and will inform the consideration of force accuracy training (FAT) as a potential intervention to improve the neuromuscular and physical function of stroke patients.

Experimental Protocol

Participants:

This study will be carried out on 16 post-stroke participants (aged 18 or over), with an aim to recruit 50% males. Before enrolment in the study, participants will complete a screening session which will include an electrocardiogram (ECG), blood pressure check, an ultrasound scan of your thigh muscles to look at their structure, and general health questions, including previous medical history.

This session will also provide potential participants an opportunity to ask any questions about the study that they may have after reading the participant information sheet (PIS). If an abnormal screening result is encountered, this will be discussed with the participant, and their GP will be informed in writing. All participants will be informed in detail about the procedures and risks of the study via the PIS and have the opportunity to ask questions before their written informed consent is obtained.

Assessment Sessions:

After the screening session, if deemed eligible, participants will be requested to attend a single assessment session. The primary endpoint of this study is neuromuscular assessment after stroke as compared with 'healthy' older adult data that we already have.

This session will last ~3 hours allowing sufficient time for an explanation of each component and will consist of:

An ultrasound of vastus lateralis muscle architecture
Isometric dynamometry to determine maximum voluntary contraction (MVC) for upper and lower limb extension and flexion, including handgrip dynamometry
High-Density Surface electromyography (HDsEMG) and intramuscular electromyography (iEMG) of the muscles of the upper (bicep, tricep and abductor digiti minimi) and lower limbs (vastus lateralis and tibialis anterior) to determine muscle activation patterns
Motor control assessments for the upper and lower limbs (i.e., force tracking tasks for knee and elbow extension)
The Grooved Pegboard Test to assess dexterity
Balance tests*
The Short Physical Performance Battery (SPPB) to assess overall physical performance*
Timed Up-and-Go (TUG) to determine mobility
Gait analysis*
Determination of a Modified Rankin Score (mRS)
Assessment against the Stroke Impact Scale
Motor functioning assessment via the Fugl-Meyer Assessment

*These assessments will not be conducted in those who use a frame to mobilise.

A member of the research team with Hospital Life Support training and certified competency in each of the above assessments will fully-supervise each session.

Measurable endpoints/ statistical power of study

As a pilot characterisation study, no formal power calculation has been performed. However, this number is similar to that reported in the literature when reporting neuromuscular differences between groups.

Risk summary:
Overall, this is a low-risk study. Pin insertion for iEMG can in some cases feel uncomfortable, although this is rare.

PARTICIPANTS

Description of study participants

16 adults over 18 years old

Inclusion criteria

Aged over 18 years old
Willing and able to give informed consent for participation in the study
Had a confirmed stroke within the last 5 years
Self-reports of a persisting post-stroke loss of unilateral limb function

Exclusion criteria

Diagnosis of cognitive impairment/dementia
Current or recent (<2y) malignancy
Severe respiratory disease (e.g., uncontrolled asthma, COPD, pulmonary hypertension)
Active cardiovascular disease: Uncontrolled hypertension (BP>160/100mmHg); Recent (<12mo) cardiac event; Heart failure (Class III/IV); Significant arrhythmia; Unstable angina
Metabolic disease: Untreated hyper/hypoparathyroidism; Cushing's disease
Significant musculoskeletal disorders (based on clinical opinion)
Dialysis patients
Recent steroid treatment within 6 months or hormone replacement therapy
Mobility dependent (wheelchair dependency)

Recruitment

Describe how potential participants will be identified, approached and recruited.

Participants will be recruited via posters at local community groups that engage with older adults per se, via our existing PPI-E networks, and via charities that work with stroke survivors. These charities include the Stroke Association and British Heart Foundation, both of whom Prof England has ongoin research activities with. Participants who express an interest will be invited for a screening session at mutually convenient time to assess their eligibility against pre-determined inclusion/exclusion criteria

Screening and eligibility assessment

Specify the maximum duration allowed between screening and recruitment (if applicable).

Before enrolment into the study, participants will complete a screening session which will include an electrocardiogram (ECG), blood pressure check, and general health questions, including previous medical history. This session will also provide potential participants an opportunity to ask any questions about the study that they may have after reading the participant information sheet (PIS). If a abnormal screening result is encountered, this will be discussed with the participant, and their GP wil be informed in writing. All participants will be informed in detail about the procedures and risks of th study via the PIS and will have the opportunity to ask questions before their written informed consent obtained. All screening results will be checked by a clinician to determine eligibility. The maximum duration between screening and first assessment visit will be 3-months, as per research group policy.

Information provided to participants and informed consent

Specify who will take informed consent, how and when it will be taken.

Participants will be given a participation information sheet (PIS) before being invited to a screening session. This document has been prepared in understandable, simple language and contains the details

of the study. Participants will be given sufficient time (>48h) to read and decide about study participation after the PIS has been given. There will be an opportunity for participants to ask the research team any questions about the study at the screening session. Written informed consent will b signed and dated by participants and the individual recording consent. A copy of the signed informed consent form will be given to participants, and the original form will be kept in the study area. Conse will only be taken by individuals after they have received study-specific consent training by Prof Phillips or Amanda Gates (Senior Clinical Measurement Technician) as per research group policy.

List the names and job roles of the investigative team members who will obtain consent:
Prof Bethan Phillips, PI
Dr Mathew Piasecki, Co-I
Prof Timothy England, Co-I
Mr Abdulmajeed Altheyab, PhD student (Physiotherapist)
Mrs Amanda Gates, Senior Clinical Measurement Technician

Participant confidentiality

Give details about how you will maintain the confidentiality of participant's personal and research data.

All study staff will ensure that the participants' data are safeguarded. The consent form for participati in the study will include the participants' name and telephone number, as well as their unique study II code. These forms will be stored in a locked cabinet at the research unit, and only personnel directly involved in the study and university personnel responsible for research audit can access these documents. All study samples and research data will be stored or saved to OneDrive with the linked-anonymised study ID code only. If any paper research data exists, this will also be saved with the stu ID code only and in a separate location to the consent form. Participants will be able express their choice about their contact details being used for the purpose of inviting them to participate in future studies on the consent form.

STUDY PROCEDURES

Baseline assessments and procedures

Following the screening session where informed consent is given and once eligibility has been confirmed by a clinician, participants will attend for their study visit as arranged by the research team for a mutually convenient time.

The following assessments will be conducted:

An ultrasound of vasus lateralis muscle architecture – to determine muscle thickness, pennation angle and fascicle length.

Isometric dynamometry to determine maximum voluntary contraction (MVC) for upper and lower limb extension and flexion, including handgrip dynamometry.

High-Density Surface electromyography (HDsEMG) and intramuscular electromyography (iEMG) of the muscles of the upper (bicep and tricep) and lower limbs (vastus lateralis and tibialis anterior) to determine muscle activation patterns. Intramuscular electromyography (iEMG and high-density sEMG (HD-sEMG) will be used to determine motor unit structure (size & number) and function (firing rate, firing complexity, neuromuscular junction transmission reliability). sEMG will also be used to determine muscle activation patterns and the largest compound muscle action potential (M-wave). This will be performed using skin electrodes (HDsEMG) and a small pin-type electrode (iEMG) inserted into the upper and lower limb muscles.

Motor control assessments for the upper and lower limbs (i.e., force tracking tasks for knee and elbow extension). Participants will be requested to follow a force trace line on a monitor during extension and flexion movements. The intensity of this force will be relative to their individual capabilities.

The Grooved Pegboard Test to assess dexterity. This simply involves participants placing small metal pegs into small holes in a specific order. This assessment is timed.

The Trail Making Test (TMT) is a timed, neuropsychological test that involves visual scanning and working memory.

Balance tests*. Using a platform that can assess features such as Centre of Pressure (COP) and sway participants will be asked to stand on both feet, and then on one foot with their eyes open and closed. Time to failure (i.e., need to place second foot on the floor and/or open eyes) will be recorded. A chai will be located behind participants for this assessment and a researcher will remain within touching distance. Participants will only be requested to complete the aspects of this assessment that they feel comfortable doing.

The Short Physical Performance Battery (SPPB) to assess overall physical performance*. The SPPB consists of tandem, semi-tandem and parallel stand time, gait speed and chair rise time (withou the use of arms).

Timed Up-and-Go (TUG) to determine mobility. This clinically validated measure of mobility requires participants to rise from a chair, walk 4m, turn and return to the chair. Any assistive devices normally used (i.e., a stick or frame) can be used during this assessment.

Gait analysis*. For this analysis participants simply have to walk over a biomechanics platform using their normal gait so that features such as stride length and stride symmetry can be assessed.

Determination of a Modified Rankin Scale (mRS) is a 7-level ordered categorical scale capturing levels of patient functional independence following a stroke, with scores ranging from 0 (fully independent) to 6 (dead).

Assessment against the Stroke Impact Scale is a patient-reported outcome measure that evaluates th biopsychosocial aspects of life after stroke.
Motor functioning assessment via the Fugl-Meyer Assessment is a stroke-specific, performance-based impairment index. It is designed to assess motor functioning, sensation, balance, joint range of motion and joint pain in patients with post-stroke hemiplegia.

*These assessments will not be conducted in those who use a frame to mobilise.

Subsequent visits

N/A

Sample handling

No bio-samples will be collected.

Discontinuation/ withdrawal of participants from the study

Outline why the study may be discontinued and/or why participants may be withdrawn from the study

Each participant has the right to withdraw from the study at any time and without giving reason. In addition, the research team may remove a participant from the study at any time if, for any reason, it considers that the participant is unsuitable for the study. Although not an exhaustive list, potential reasons for exclusion include:

• Ineligibility (from situations that may arise during the study and reasons that may have been overlooked in the evaluation)
• Withdrawal of Consent
• Non-attendance at assessment session

If the data of participants who withdraw/are excluded from the study will be included in study dissemination will depend on how much data is collected at that stage. If the data is insufficient, it wi be excluded from the study. Withdrawn participants will be replaced to ensure an optimal number of participants complete the study. Any reason for withdrawal will be added to the study records.

If a participant is withdrawn due to an adverse event, specify any procedures and/or observations tha will continue until resolution of the event. Why will this be necessary?

If any previously unknown signs of medical conditions are discovered during the screening or study, clinician will contact the participant and their GP will be informed. Any adverse events that occur

during the study will be followed up by the research team until they are resolved, they will be recorde in the study records and if required (i.e., serious adverse event), will be reported to the FMHS REC.

Definition of end of study

Define the end of study for participant involvement.

The end of the study will be the last participant's assessment visit.

Expenses and benefits

Please detail all expenses or gifts (vouchers, certificates etc.) that will be afforded to participants for taking part and how this will be affected if they do not complete the study.

All participants will be given a report of their assessment visit data if they wish. In addition, all participants who complete the study will be given an inconvenience allowance of £50. If participants withdraw before the end of the study for reasons not related to the study, they will receive an inconvenience allowance relative to their duration of involvement at the discretion of the study PI. Th is unlikely as this study involves a single assessment visit only.

INTERVENTION(S) & DRUG ADMINISTRATION

Drug/ Substance/ Intervention 1

Name of drug/ substance/ intervention to be used	N/A
Formulation and route of administration for study	N/A
Dose and route of administration for study	N/A
Duration of treatment for study	N/A
Licence status of this drug/substance	N/A
Usual indication	N/A
Usual dose	N/A
Usual duration of treatment	N/A
Where will drug/ substance be sourced from?	N/A
Where will drug/substance be stored?	N/A
How will drug/substance be dispensed?	N/A
How will the drug/ substance be prepared by the researchers for use in this study?	N/A

SAFETY

a)Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a substance ha been administered, including occurrences which are not necessarily caused by or related to that substance.
Adverse Reaction (AR)	An untoward and unintended response in a participant to a substance, whic is related to any dose administered to that participant. A causal relationship between the administered substance and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the stu intervention qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: results in death is life-threatening requires inpatient hospitalisation or prolongation of existing hospitalisation results in persistent or significant disability/incapacity consists of a congenital anomaly or birth defect. Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to a event in which the participant was at risk of death at the time of the event;

	does not refer to an event which hypothetically might have caused death if were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consiste with the information about the medicinal product set out in its summary of product characteristics (SmPC).

Reporting Procedures for Serious Adverse Events or Reactions
A serious adverse event (SAE) occurring to a participant should be reported to UoN FMHS UREC where, in the opinion of the PI, the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' (the type of event is not listed on this form as an expected occurrence). Reports of related and unexpected SAE's should be submitted by the PI within 7 days of the event. For fatal and life-threatening SUSARs, this will be done no later than 3 calendar days after the Sponsor or PI is first aware of the reaction. Any additional relevant information will be reported within 7 calendar days of the initial report.

Safety of Participants

What level of baseline screening will take place for this study?
Before enrolling, participants will attend a screening visit to verify their eligibility for the study. Duri this screening visit, medical history, electrocardiogram (ECG) and blood pressure (BP) will be recorded. Based on the screening data, the participant will be reviewed by a clinician to make sure it i suitable for them to participate. Participants will also be given a chance to ask questions about the stu before giving their informed consent.
Provide details about the safety monitoring of participants and the staff/researchers carrying th out
During the assessment days, participants will always be accompanied by a member of the research team. Where possible, email will be used to communicate with participants over the course of the study, although participants will also be given an office phone number to contact the research team.
Give details on the medical cover required and who will provide this cover
A clinician will have the final decision on participant eligibility with Prof Tim England providing clinical oversight for this study. Beyond this, given the nature of the assessment sessions and as per th research group policy, medical cover will not be needed for the assessment days. However, for all of these visits, participants will be with a member of the research team who has basic/hospital life-suppo certification (BLS/HLS)- with another BLS/HLS-trained member of the research team immediately contactable.
Will the participants' GP be informed about their participation in the study?
This would be regarded as essential if the study includes consumption of drugs or novel chemical entities or if you are recommending that the volunteer should see their GP as a result of the study. No, GP's will only be contacted if there is an incidental finding.
What is your planned procedure if an incidental finding is suspected?

If an undiagnosed condition is discovered during screening or study participation, a member of the research team will contact the participant and inform their GP.

Ethical Considerations

Most research carries the risk of some ethical challenge. If this is the case you need to demonstrate your awareness of the problem and your response to mitigate ethical objections. There is a free text box below to detail any study specific ethical issues, however the following areas are often a cause for concern:

Will you include any vulnerable participants? (e.g. children (under 16 years old) or vulnerable adults with a mental incapacity or prisoners) **If yes,** please describe how they are defined as vulnerable and detail any approved procedures or guidance that you feel apply.	Yes ☒	No
Although participants in this study are community-dwelling, their age and past stroke may mean that some respects they are considered vulnerable. All participants will be supervised at all times and will be invited to bring an additional person (i.e., friend, partner, carer etc.) to both their research visits (screening and assessment). All of the investigators for this study have significant experience conducting research in older adults, with Prof England also having vast experience with stroke patien		
Will taking part in the research put participants under any particular burden and/ or risk? **If yes,** describe how this will be mitigated.	Yes ☒	No
There is a time commitment to participation in this study, however participation is voluntary, and an inconvenience allowance is provided. There is a small risk that unaccustomed contractile activity ma cause muscle soreness, but this is unlikely given the low volume. Similarly, the pin electrode for EM may be uncomfortable at the point of insertion but this is not reported by many.		
Will the research involve deliberate *deception* of participants? **If yes**, justify why deception is used, describe deception and debriefing process, and include debriefing documents in the application.	Yes ☐	No
N/A		
Will any procedures affect your own or any member of the research teams physical and/ or psychological safety as a researcher? **If yes,** describe how this will be mitigated.	Yes ☐	No
N/A		
Does your research raise issues relevant to the Counter-Terrorism and Security Act (the Prevent Duty), which seeks to prevent people from being drawn into terrorism? **If yes,** please say how you plan to address any related risks.	Yes ☐	No
N/A		
Please give details of any other study-specific ethical and/or safety considerations.		
No issues beyond those outlined above.		

STATISTICS AND ANALYSIS

Do you have a statistical plan? **If no,** please justify.	Yes ☒	No
Data analysis will be performed using GraphPad Prism Version 11 (GraphPad Software, CA, USA) f multi-level mixed effects regression models for group vs. limb. The baseline characteristics of participants will be compared by independent t-test. All data will be presented as mean +/- SEM. Significance level will be set at $p<0.05$.		
Number of participants & group allocations		
16 post-stroke participants to be compared to baseline data from an age-matched study of force accuracy training.		
Have you done a sample size calculation? If yes, please give details below. If no, please give details to indicate you have considered the implications the selected sample size will have on the study outcome.	Yes ☐	No
As a pilot characterisation study, no formal power calculation has been performed. However, this number is similar to that reported in the literature when reporting neuromuscular differences betwee groups.		
Analysis of Outcome Measures		
EMG and functional parameters will be analysed using previously established methods (Piasecki et a 2018), with EMG data acquired in Spike and DQEMG software and sEMG data analysed using MATLAB (DEMUSE). Multi-level mixed-effects models will be applied to populations of motor uni from each participant, for each limb.		

DATA MANAGEMENT

Summary for Form

Who will have access to the *research* data?	All members of the research team will have access to anonymized research data. These data will be used in thesis, journal articles and conference presentations. Direct access to identifiable data and research data wil also be granted to authorised representatives from the University of Nottingham for monitoring and/or audit the study to ensure compliance with regulations.
How will *research* data be stored?	Identifiable and anonymized paper documents will be stored in separate folders in a locked cabinet at the University of Nottingham Medical School at Derby. Electronic information will be stored anonymously on password protected computers with regular automated back-up (OneDrive).
How long will *research* data be stored for?	All research data will be kept securely for 7 years.
What will be done with the *research* data at the end of the storage period?	This will be deleted and/or disposed of securely.
Who will have access to the participants' *personal* data?	Access to personal (identifiable) information is limited only to research staff involved in the participation elements of this study, and to audit staff as detailed above.
How will *personal* data be stored?	Personal data will be stored in a locked cabinet at the University of Nottingham Medical School at Derby. Personal data will be kept separate from research data
How long will *personal* data be stored for?	To comply with the data protection act, personal data will be deleted as soon as possible after it is no longer needed for the study. If the participants consent to be contacted for another study in the future, the contact information of the participants will be stored separatel from the research data for 5 years.
Describe method(s) of research data entry/management	All study data collected on paper during the assessmer visits (i.e., balance time) will be anonymized and save in an Excel spreadsheet. Each participant will be giver study specific ID code and all research data will be recorded with this code. All computer-generated data will also be stored against this code before being entered/exported to Excel as appropriate.

Please use the Data Management Plan online Tool https://dmponline.dcc.ac.uk/ and generic UoN template.

STUDY MONITORING AND OVERSIGHT

Who will be responsible for day-to-day supervision of the study?
Prof Bethan Phillips
Give information about frequency of meetings that will be held to discuss progress/problems. Who will be present at the meetings?
Monthly meetings will be held with the PhD student and one or more other members of the research team, or more frequently if necessary.

ETHICAL AND REGULATORY CONSIDERATIONS

Declaration of Helsinki

The PI will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

Approvals

This form, an informed consent form, a participant information sheet and any proposed advertising material will be submitted to the UoN FMHS REC for written approval. The research team will submit and, where necessary, obtain approval from the UoN FMHS REC and any other above-mentioned parties for all amendments to the original approved documents.

End-of-Study Report

The PI shall request, complete and submit an end-of-study report to the UoN FMHS REC within 6 months of the study end (participant involvement).

DISSEMINATION AND FEEDBACK OF STUDY OUTCOMES

Please describe your plans with respect to participants as well as public dissemination plans, e.g., in journals and conferences. If the study results form part of a Master's or DPhil dissertation, please give details here. Consider describing how study results may be disseminated to study participants.

It is anticipated that the data collected during this study will be part of a PhD thesis and will also be published in open-access peer reviewed scientific/clinical journals. Prior to publication it is anticipated that aspects of this work will also be presented at academic conferences. Given the nature of this work, we also intend to practice stakeholder dissemination (including community outreach) to inform those involved in care of stroke patients of the findings of this work.

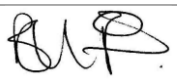
REFERENCES

Insert references used in text in number or alphabetical order (excluding those already listed in Section 4).

No further references

DECLARATIONS AND SIGNATURES

I/ we, the researcher(s) agree:
To start this research study only after obtaining approval from the UoN FMHS REC;
To carry out this research study only if funding is adequate to enable it to be carried out according to good research practice and in an ethical manner;
That it is the responsibility of the PI to ensure that all researchers working on this project are qualified and either experienced, or have received appropriate training (including ethical training), to conduct the research described;
To provide additional information as requested by UoN FMHS REC before approval is secured and as research progresses;
To maintain the confidentiality of all data collected from or about study participants;
To notify UoN FMHS REC in writing immediately of any proposed change which would increase the risk or burden that any participant is exposed to, and await approval before proceeding with the proposed change;
To notify UoN FMHS REC if the PI on the study changes and supply the name of the successor;
To notify UoN FMHS REC in writing within seven days if any serious adverse event occurs in the course of research;
To use data collected only for the study for which approval has been given;
To grant access to data only to authorised persons; and
To maintain security procedures for the protection of personal data, including (but not restricted to): removal of identifying information from data collection forms and computer files, storage of linkage codes in a locked cabinet, and password control for access to identified data on computer files.

Principal Investigator (Name)	Professor Beth Phillips
Principal Investigator (Signature)	
Medically qualified collaborator (Name)	Prof Tim England
Medically qualified collaborator (Signature)	
Student (Name)	Mr. Abulmajeed Altheyab
Student (Signature)	

CHECKLIST: (mark as complete (X) or non-applicable (N/A):

Completed form signed by the PI **X**
Data Management Plan **X**
Participant information sheet (PIS) **X**
Informed consent form (ICF) **X**
Poster or advert or draft of text to be used in social media **X**

Applications must be submitted to: FMHS REC Administrator– FMHS-ResearchEthics@nottingham.ac.uk **at least two weeks before the meeting.** This is necessary to ensure that all members of the Committee can adequately review the application. Applications received after this time will be held over until the following meeting. Approval cannot be given to protocols by Chair's action.*

*Except Studies involving blood taking only, where the information generated is of no prognostic significance (i.e. for lab based cell biology studies) These studies will be approved by Chair's action provided no more than a total of 500mls of blood is taken over a 6-month period and no more than 200mls is taken on a single occasion. For these studies applicants need to submit 1 copy of this form and the other required documentation plus a cover letter detailing the nature of the study.

AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

List details of all protocol amendments here whenever a new version of an approved document is produced
This is not necessary prior to initial REC submission

University of Nottingham
UK | CHINA | MALAYSIA

Faculty of Medicine & Health Sciences
Research Ethics Committee
Faculty Hub
Room E41, E Floor, Medical School
Queen's Medical Centre Campus
Nottingham University Hospitals
Nottingham, NG7 2UH
Email: FMHS-ResearchEthics@nottingham.ac.uk

04 June 2024

Abdulmajeed Altheyab
Postgraduate Researcher/PhD
MRC-Versus Arthritis Centre for Musculoskeletal Ageing Research
Centre for Metabolism, Ageing & Physiology (COMAP)
School of Medicine, University of Nottingham
Royal Derby Hospital Centre
Uttoxeter Road, Derby
DE22 3DT

Dear Mr Altheyab

Ethics Reference No: FMHS 188-0524 – please always quote	
Study Title: Characterising the neuromuscular function of stroke patients during recovery (cSTROKE)	
Chief Investigator/Supervisor: Bethan Phillips, Professor of Translational Physiology, COMAP, Injury, Recovery and Inflammation Sciences (IRIS), School of Medicine	
Lead Investigators/student: Abdulmajeed Altheyab, Postgraduate Researcher/PhD, COMAP, IRIS, School of Medicine	
Other Key investigators: Mathew Piasecki, Associate Professor of Neuromuscular Physiology, COMAP, IRIS, Timothy England, Professor of Stroke Medicine, Translational Medical Sciences, School of Medicine.	
Proposed Start Date: 01/05/2024	**Proposed End Date:** 01/05/2026

Thank you for submitting the above application. This was considered at the Committee Meeting held on 24 May 2024. The following documents were received:

- FMHS REC Application form and supporting documents version 1.0: 11.03.2024

These have been reviewed and are satisfactory and the project is given a favourable research ethics opinion.

A favourable research ethics opinion is given on the understanding that:

1. All gatekeeper permissions for posting adverts are checked if required and are in place before recruitment starts.
2. The protocol agreed is followed and the Committee is informed of any changes using a notice of amendment form (please request a form).
3. The Chair is informed of any serious or unexpected event.
4. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely

Dr John Williams, Associate Professor in Anaesthesia and Pain Medicine
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

Outlook

ClinicalTrials.gov Protocol Record FMHS 188-0524

From ClinicalTrials.gov Registration <register@clinicaltrials.gov>
Date Mon 2025-06-09 7:12 PM
To Abdulmajeed Altheyab <mzxaa27@exmail.nottingham.ac.uk>
Cc register@clinicaltrials.gov <register@clinicaltrials.gov>; Beth Phillips (staff) <mbzbp@exmail.nottingham.ac.uk>; Beth Phillips (staff) <mbzbp@exmail.nottingham.ac.uk>

Message generated by ClinicalTrials.gov Protocol Registration and Results System

ClinicalTrials.gov Identifier: NCT07013188

University of Nottingham Protocol Record FMHS 188-0524,
Characterising the Neuromuscular Function of Post Stroke Patients,
is registered and will be posted on the ClinicalTrials.gov public website.

RECORDS USUALLY APPEAR ON ClinicalTrials.gov WITHIN 2 BUSINESS DAYS
of the receipt of this message.

QUESTIONS? Contact us at: register@clinicaltrials.gov

Thank you,

PRS Team
ClinicalTrials.gov

Modified Rankin Scale (mRS)

Patient's Full Name: _____ **Date Rated:** _____

Rater's Full Name: _____

Instructions

- Schedule an interview with your patient and/or their caregivers and loved ones
- During the interview, ask about how the patient is feeling and if they are able to do activities of daily living as well as other activities they normally do
- Observe them, if you can, especially if they are doing some ADLs, with or without support

Patient Rating

- ○ **0 =** The patient has no symptoms at all.
- ○ **1 =** The patient has no significant disability despite symptoms. They are able to carry out all their usual duties and activities.
- ○ **2 =** The patient has a slight disability. They are unable to carry out all previous pre-stroke activities, but they are able to look after their own affairs without assistance.
- ○ **3 =** The patient has a moderate disability. They also require some help, but they are able to walk without assistance.
- ○ **4 =** The patient has a moderately severe disability. They are also unable to walk without assistance and they are unable to attend to their own bodily needs without assistance.
- ○ **5 =** The patient has a severe disability. They are bedridden, incontinent, and they require constant nursing care and attention.
- ○ **6 =** The patient is dead.

Additional Comments

References:

Rankin J. “Cerebral vascular accidents in patients over the age of 60.” Scott Med J 1957;2:200-15
Bonita R, Beaglehole R. “Modification of Rankin Scale: Recovery of motor function after stroke.” Stroke 1988 Dec;19(12):1497-1500

https://Carepatron.com

Powered by carepatron

The purpose of this questionnaire is to evaluate how stroke has impacted your health and life. We want to know from **YOUR POINT OF VIEW** how stroke has affected you. We will ask you questions about impairments and disabilities caused by your stroke, as well as how stroke has affected your quality of life. Finally, we will ask you to rate how much you think you have recovered from your stroke.

Stroke Impact Scale

These questions are about the physical problems which may have occurred as a result of your stroke.

1. In the past week, how would you rate the strength of your....	**A lot of strength**	**Quite a bit of strength**	**Some strength**	**A little strength**	**No strength at all**
a. Arm that was most affected by your stroke?	5	4	3	2	1
b. Grip of your hand that was most affected by your stroke?	5	4	3	2	1
c. Leg that was most affected by your stroke?	5	4	3	2	1
d. Foot/ankle that was most affected by your stroke?	5	4	3	2	1

These questions are about your memory and thinking.

2. In the past week, how difficult was it for you to...	**Not difficult at all**	**A little difficult**	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
a. Remember things that people just told you?	5	4	3	2	1
b. Remember things that happened the day before?	5	4	3	2	1
c. Remember to do things (e.g. keep scheduled appointments or take medication)?	5	4	3	2	1
d. Remember the day of the week?	5	4	3	2	1
e. Concentrate?	5	4	3	2	1
f. Think quickly?	5	4	3	2	1
g. Solve everyday problems?	5	4	3	2	1

These questions are about how you feel, about changes in your mood and about your ability to control your emotions since your stroke.

3. In the past week, how often did you...	**None of the time**	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**
a. Feel sad?	5	4	3	2	1
b. Feel that there is nobody you are close to?	5	4	3	2	1
c. Feel that you are a burden to others?	5	4	3	2	1
d. Feel that you have nothing to look forward to?	5	4	3	2	1
e. Blame yourself for mistakes that you made?	5	4	3	2	1
f. Enjoy things as much as ever?	5	4	3	2	1
g. Feel quite nervous?	5	4	3	2	1
h. Feel that life is worth living?	5	4	3	2	1
i. Smile and laugh at least once a day?	5	4	3	2	1

The following questions are about your ability to communicate with other people, as well as your ability to understand what you read
and what you hear in a conversation.

4. In the past week, how difficult was it to...	**Not difficult at all**	**A little difficult**	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
a. Say the name of someone who was in front of you?	5	4	3	2	1
b. Understand what was being said to you in a conversation?	5	4	3	2	1
c. Reply to questions?	5	4	3	2	1
d. Correctly name objects?	5	4	3	2	1
e. Participate in a conversation with a group of people?	5	4	3	2	1
f. Have a conversation on the telephone?	5	4	3	2	1
g. Call another person on the telephone, including selecting the correct phone number and dialing?	5	4	3	2	1

The following questions ask about activities you might do during a typical day.

5. In the past 2 weeks, how difficult was it to...	**Not difficult at all**	**A little difficult**	**Somewhat difficult**	**Very difficult**	**Could not do at all**
a. Cut your food with a knife and fork?	5	4	3	2	1
b. Dress the top part of your body?	5	4	3	2	1
c. Bathe yourself?	5	4	3	2	1
d. Clip your toenails?	5	4	3	2	1
e. Get to the toilet on time?	5	4	3	2	1
f. Control your bladder (not have an accident)?	5	4	3	2	1
g. Control your bowels (not have an accident)?	5	4	3	2	1
h. Do light household tasks/chores (e.g. dust, make a bed, take out garbage, do the dishes)?	5	4	3	2	1
i. Go shopping?	5	4	3	2	1
j. Do heavy household chores (e.g. vacuum, laundry or yard work)?	5	4	3	2	1

The following questions are about your ability to be mobile, at home and in the community.

6. In the past 2 weeks, how difficult was it to...	**Not difficult at all**	**A little difficult**	**Somewhat difficult**	**Very difficult**	**Could not do at all**
a. Stay sitting without losing your balance?	5	4	3	2	1
b. Stay standing without losing your balance?	5	4	3	2	1
c. Walk without losing your balance?	5	4	3	2	1
d. Move from a bed to a chair?	5	4	3	2	1
e. Walk one block?	5	4	3	2	1
f. Walk fast?	5	4	3	2	1
g. Climb one flight of stairs?	5	4	3	2	1
h. Climb several flights of stairs?	5	4	3	2	1
i. Get in and out of a car?	5	4	3	2	1

The following questions are about your ability to use your hand that was MOST AFFECTED by your stroke.

7. In the past 2 weeks, how difficult was it to use your hand that was most affected by your stroke to...	**Not difficult at all**	**A little difficult**	**Somewhat difficult**	**Very difficult**	**Could not do at all**
a. Carry heavy objects (e.g. bag of groceries)?	5	4	3	2	1
b. Turn a doorknob?	5	4	3	2	1
c. Open a can or jar?	5	4	3	2	1
d. Tie a shoe lace?	5	4	3	2	1
e. Pick up a dime?	5	4	3	2	1

The following questions are about how stroke has affected your ability to participate in the activities that you usually do, things that are meaningful to you and help you to find purpose in life.

8. During the past 4 weeks, how much of the time have you been limited in...	**None of the time**	**A little of the time**	**Some of the time**	**Most of the time**	**All of the time**
a. Your work (paid, voluntary or other)	5	4	3	2	1
b. Your social activities?	5	4	3	2	1
c. Quiet recreation (crafts, reading)?	5	4	3	2	1
d. Active recreation (sports, outings, travel)?	5	4	3	2	1
e. Your role as a family member and/or friend?	5	4	3	2	1
f. Your participation in spiritual or religious activities?	5	4	3	2	1
g. Your ability to control your life as you wish?	5	4	3	2	1
h. Your ability to help others?	5	4	3	2	1

9. Stroke Recovery

On a scale of 0 to 100, with 100 representing full recovery and 0 representing no recovery, how much have you
recovered from your stroke?

_____ 100 Full Recovery

_____ 90

_____ 80

_____ 70

_____ 60

_____ 50

_____ 40

_____ 30

_____ 20

_____ 10

_____ 0 No Recovery

FUGL-MEYER ASSESSMENT ID:
UPPER EXTREMITY (FMA-UE) Date:
Assessment of sensorimotor function Examiner:

http://www.kumc.edu/school-of-medicine/preventive-medicine-and-public-health/research-and-community-engagement/stroke-impact-scale.html

A. UPPER EXTREMITY, sitting position			
I. Reflex activity	**none**	**can be elicited**	
Flexors: biceps and finger flexors (at least one) **Extensors**: triceps	0 0	2 2	
Subtotal I (max 4)			
II. Volitional movement within synergies, without gravitational help	**none**	**partial**	**full**

Flexor synergy: Hand from contralateral knee to ipsilateral ear. From extensor synergy (shoulder adduction/ internal rotation, elbow extension, forearm pronation) to flexor synergy (shoulder abduction/ external rotation, elbow flexion, forearm supination).	Shoulder	retraction elevation abduction (90°) external rotation flexion supination	0 0 0 0 0 0	1 1 1 1 1 1	2 2 2 2 2 2
	Elbow				
	Forearm				
Extensor synergy: Hand from ipsilateral ear to the contralateral knee	Shoulder Elbow Forearm	adduction/internal rotation extension pronation	0 0 0	1 1 1	2 2 2
Subtotal II (max 18)					

III. Volitional movement mixing synergies, without compensation		**none**	**partial**	**full**
Hand to lumbar spine hand on lap	cannot perform or hand in front of ant-sup iliac spine hand behind ant-sup iliac spine (without compensation) hand to lumbar spine (without compensation)	0	1	2
Shoulder flexion 0°- 90° elbow at 0° pronation-supination 0°	immediate abduction or elbow flexion abduction or elbow flexion during movement flexion 90°, no shoulder abduction or elbow flexion	0	1	2
Pronation-supination elbow at 90° shoulder at 0°	no pronation/supination, starting position impossible limited pronation/supination, maintains starting position full pronation/supination, maintains starting position	0	1	2
Subtotal III (max 6)				

IV. Volitional movement with little or no synergy		**none**	**partial**	**full**
Shoulder abduction 0 - 90° elbow at 0° forearm neutral	immediate supination or elbow flexion supination or elbow flexion during movement abduction 90°, maintains extension and pronation	0	1	2
Shoulder flexion 90° - 180° elbow at 0° pronation-supination 0°	immediate abduction or elbow flexion abduction or elbow flexion during movement flexion 180°, no shoulder abduction or elbow flexion	0	1	2
Pronation/supination elbow at 0° shoulder at about 30° flexion	no pronation/supination, starting position impossible limited pronation/supination, maintains start position full pronation/supination, maintains starting position	0	1	2
Subtotal IV (max 6)				

V. Normal reflex activity assessed only if full score of 6 points is achieved in part IV; compare with the unaffected side		**hyper**	**lively**	**normal**
Biceps, triceps, finger flexors	2 of 3 reflexes markedly hyperactive 1 reflex markedly hyperactive or at least 2 reflexes lively maximum of 1 reflex lively, none hyperactive	0	1	2
Subtotal V (max 2)				
Total A (max 36)				

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B. WRIST support may be provided at the elbow to take or hold the starting position, no support at wrist, check the passive range of motion prior testing		**none**	**partial**	**full**
Stability at 15° dorsiflexion elbow at 90°, forearm pronated shoulder at 0°	less than 15° active dorsiflexion dorsiflexion 15°, no resistance tolerated maintains dorsiflexion against resistance	0	1	2
Repeated dorsifexion / volar flexion elbow at 90°, forearm pronated shoulder at 0°, slight finger flexion	cannot perform volitionally limited active range of motion full active range of motion, smoothly	0	1	2
Stability at 15° dorsiflexion elbow at 0°, forearm pronated slight shoulder flexion/abduction	less than 15° active dorsiflexion dorsiflexion 15°, no resistance tolerated maintains dorsiflexion against resistance	0	1	2
Repeated dorsifexion / volar flexion elbow at 0°, forearm pronated slight shoulder flexion/abduction	cannot perform volitionally limited active range of motion full active range of motion, smoothly	0	1	2
Circumduction elbow at 90°, forearm pronated shoulder at 0°	cannot perform volitionally jerky movement or incomplete complete and smooth circumduction	0	1	2
Total B (max 10)				

C. HAND support may be provided at the elbow to keep 90° flexion, no support at the wrist, compare with unaffected hand, the objects are interposed, active grasp		**none**	**partial**	**full**
Mass flexion from full active or passive extension		0	1	2
Mass extension from full active or passive flexion		0	1	2
GRASP				
a. Hook grasp flexion in PIP and DIP (digits II-V), extension in MCP II-V	cannot be performed can hold position but weak maintains position against resistance	0	1	2
b. Thumb adduction 1-st CMC, MCP, IP at 0°, scrap of paper between thumb and 2-nd MCP joint	cannot be performed can hold paper but not against tug can hold paper against a tug	0	1	2
c. Pincer grasp, opposition pulpa of the thumb against the pulpa of 2-nd finger, pencil, tug upward	cannot be performed can hold pencil but not against tug can hold pencil against a tug	0	1	2
d. Cylinder grasp cylinder shaped object (small can) tug upward, opposition of thumb and fingers	cannot be performed can hold cylinder but not against tug can hold cylinder against a tug	0	1	2
e. Spherical grasp fingers in abduction/flexion, thumb opposed, tennis ball, tug away	cannot be performed can hold ball but not against tug can hold ball against a tug	0	1	2
Total C (max 14)				

D. COORDINATION/SPEED, sitting, after one trial with both arms, eyes closed, tip of the index finger from knee to nose, 5 times as fast as possible		**marked**	**slight**	**none**
Tremor		0	1	2
Dysmetria	pronounced or unsystematic slight and systematic no dysmetria	0	1	2
		≥ 6s	**2 - 5s**	**< 2s**
Time start and end with the hand on the knee	6 or more seconds slower than unaffected side 2-5 seconds slower than unaffected side less than 2 seconds difference	0	1	2
Total D (max 6)				

TOTAL A-D (max 66)	

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H. SENSATION, upper extremity eyes closed, compared with the unaffected side		**anesthesia**	**hypoesthesia or dysesthesia**	**normal**
Light touch	upper arm, forearm palmary surface of the hand	0 0	1 1	2 2
		less than 3/4 correct or absence	**3/4 correct or considerable difference**	**correct 100%, little or no difference**
Position small alterations in the position	shoulder elbow wrist thumb (IP-joint)	0 0 0 0	1 1 1 1	2 2 2 2
Total H (max12)				

I. PASSIVE JOINT MOTION, upper extremity, sitting position, compare with the unaffected side				**J. JOINT PAIN** during passive motion, upper extremity		
	only few degrees (less than 10° in shoulder)	decreased	normal	pronounced pain during movement or very marked pain at the end of the movement	some pain	no pain
Shoulder Flexion (0° - 180°) Abduction (0°-90°) External rotation Internal rotation	0 0 0 0	1 1 1 1	2 2 2 2	0 0 0 0	1 1 1 1	2 2 2 2
Elbow Flexion Extension	0 0	1 1	2 2	0 0	1 1	2 2
Forearm Pronation Supination	0 0	1 1	2 2	0 0	1 1	2 2
Wrist Flexion Extension	0 0	1 1	2 2	0 0	1 1	2 2
Fingers Flexion Extension	0 0	1 1	2 2	0 0	1 1	2 2
Total (max 24)				**Total** (max 24)		

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A. UPPER EXTREMITY	/36
B. WRIST	/10
C. HAND	/14
D. COORDINATION / SPEED	/ 6
TOTAL A-D (motor function)	/66

H. SENSATION	/12
I. PASSIVE JOINT MOTION	/24
J. JOINT PAIN	/24

FUGL-MEYER ASSESSMENT ID:
LOWER EXTREMITY (FMA-LE) Date:
Assessment of sensorimotor function Examiner:

Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S: The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. Scand J Rehabil Med 1975, 7:13-31.

E. LOWER EXTREMITY					
I. Reflex activity, supine position			**none**	**can be elicited**	
Flexors: knee flexors **Extensors**: patellar, achilles (at least one)			0 0	2 2	
Subtotal I (max 4)					
II. Volitional movement within synergies supine position			**none**	**partial**	**full**
Flexor synergy: Maximal hip flexion (abduction/external rotation), maximal flexion in knee and ankle joint (palpate distal tendons to ensure active knee flexion).	Hip Knee Ankle	flexion flexion dorsiflexion	0 0 0	1 1 1	2 2 2
Extensor synergy: From flexor synergy to the hip extension/adduction, knee extension and ankle plantar flexion. Resistance is applied to ensure active movement, evaluate both movement and strength (compare with the unaffected side)	Hip Knee Ankle	extension adduction extension plantar flexion	0 0 0 0	1 1 1 1	2 2 2 2
Subtotal II (max 14)					
III. Volitional movement mixing synergies sitting position, knee 10cm from the edge of the chair/bed			**none**	**partial**	**full**
Knee flexion from actively or passively extended knee	no active motion less than 90° active flexion, palpate tendons of hamstrings more than 90° active flexion		0	1	 2
Ankle dorsiflexion compare with unaffected side	no active motion limited dorsiflexion complete dorsiflexion		0	1	2
Subtotal III (max 4)					
IV. Volitional movement with little or no synergy standing position, hip at 0°			**none**	**partial**	**full**
Knee flexion to 90° hip at 0°, balance support is allowed	no active motion or immediate, simultaneous hip flexion less than 90° knee flexion and/or hip flexion during movement at least 90° knee flexion without simultaneous hip flexion		0	1	2
Ankle dorsiflexion compare with unaffected side	no active motion limited dorsiflexion complete dorsiflexion		0	1	2
Subtotal IV (max 4)					
V. Normal reflex activity supine position, assessed only if full score of 4 points is achieved in part IV, compare with the unaffected side			**hyper**	**lively**	**normal**
Reflex activity knee flexors, Patellar, Achilles,	2 of 3 reflexes markedly hyperactive 1 reflex markedly hyperactive or at least 2 reflexes lively maximum of 1 reflex lively, none hyperactive		0	1	2
Subtotal V (max 2)					
Total E (max 28)					

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F. COORDINATION/SPEED, supine, after one trial with both legs, eyes closed, heel to knee cap of the opposite leg, 5 times as fast as possible		**marked**	**slight**	**none**
Tremor		0	1	2
Dysmetria	pronounced or unsystematic slight and systematic no dysmetria	0	1	2
		≥ 6s	**2 - 5s**	**< 2s**
Time	6 or more seconds slower than unaffected side 2-5 seconds slower than unaffected side less than 2 seconds difference	0	1	2
Total F (max 6)				

H. SENSATION, lower extremity eyes closed, compare with the unaffected side		**anesthesia**	**hypoesthesia or dysesthesia**	**normal**
Light touch	leg foot sole	0 0	1 1	2 2
		less than 3/4 correct or absence	**3/4 correct or considerable difference**	**correct 100%, little or no difference**
Position small alterations in the position	hip knee ankle great toe (IP-joint)	0 0 0 0	1 1 1 1	2 2 2 2
Total H (max12)				

I. PASSIVE JOINT MOTION, lower extremity supine position, compare with the unaffected side		only few degrees (<10° hip)	decreased	normal
Hip	Flexion Abduction External rotation Internal rotation	0 0 0 0	1 1 1 1	2 2 2 2
Knee	Flexion Extension	0 0	1 1	2 2
Ankle	Dorsiflexion Plantar flexion	0 0	1 1	2 2
Foot	Pronation Supination	0 0	1 1	2 2
Total (max 20)				

J. JOINT PAIN during passive motion, lower extremity			
pronounced pain during movement or very marked pain at the end of the movement	some pain	no pa	
0 0 0 0	1 1 1 1	2 2 2 2	
0 0	1 1	2 2	
0 0	1 1	2 2	
0 0	1 1	2 2	
Total (max 20)			

E. LOWER EXTERMTY	/28
F. COORDINATION / SPEED	/6
TOTAL E-F (motor function)	/34

H. SENSATION	/12
I. PASSIVE JOINT MOTION	/20

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J. JOINT PAIN	/20