Investigation of Upper Limb Kinematics and Corticospinal Pathway Activity Early After Stroke

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Abstract

Reach-to-grasp is an essential part of activities of daily living (ADL's); despite rehabilitation reach-to-grasp often impaired after a stroke contributing to disability. Upper limb rehabilitation interventions need improvement. A deeper understanding of underlying kinematic characteristics and the neural correlates of movement can be achieved through neuro-biomechanical assessment. This would provide knowledge of the interaction of the nervous and musculoskeletal system, which may contribute to development of improved targeted upper limb interventions.

A systematic review and meta-analysis was conducted investigating the kinematic differences in reach-to-grasp between stroke survivors and neurologically intact adults. The results indicate stroke survivors consistently demonstrate different kinematics to neurologically intact adults during reach-to-grasp in the central and ipsilateral workspace. There was heterogeneity of the reach-to-grasp task, and included studies demonstrated unclear or high potential risk of bias.

A test-retest reliability study investigated transcranial magnetic stimulation (TMS) measures of corticospinal pathway excitability in the bilateral biceps, extensor carpi radialis (ECR), and abductor pollicis brevis (APB) in neurologically intact adults. The results demonstrate variable reliability; the lower end of the confidence interval was below acceptable reliability (ICC < 0.70) for many measures. The 95% confidence intervals (CI) and 95% limits of agreement (LOA) were wide, further indicating imprecision in measurement.

A test-retest reliability study investigated TMS measures of corticospinal pathway excitability in the bilateral biceps, ECR and APB in stroke survivors within three months after stroke. The results demonstrate variable reliability; and the lower end of the confidence interval was below the range of acceptable reliability (ICC < 0.70) for many measures. The 95% CI and 95% LOA were wide, further indicating imprecision in measurement.

Investigations into the variability of TMS measures in sub-acute stroke survivors and neurologically intact adults; as well as specificity of TMS measurement warrant future investigations to determine the use of TMS within these populations.

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Table 1- Table of Abbreviations

Definition	Abbreviation
Activities of Daily Living	ADL
Active Motor Threshold	AMA
Action Research Arm Test	ARAT
Brain Derived Neurotrophic Factor	BDNF
Central nervous System	CNS
Diffusion Tensor Imaging	DTI
Electromyography	EMG
Functional Magnetic Resonance Imaging	fMRI
Gamma-aminobutyric acid	GABA
Limits of Agreement	LOA
Long Term Depression	LTD
Long Term Potentiation	LTP
Magnetoencephalography	MEG
Motor Evoked Potentials	MEP
N-Methyl-D-Aspartate receptor	NMDA
Paired Associative Stimulation	PAS
Peripheral Nervous System	PNS
Paired Pulse Transcranial Magnetic Stimulation	ppTMS
Resting Motor Threshold	RMT
Repetitive Transcranial Magnetic Stimulation	rTMS
Theta Burst Stimulation	TBS
Transcranial Magnetic Stimulation	TMS
United Kingdom	UK
Wolf Motor Function Test	WMFT

Table 1 Describes the abbreviations and their associated definitions used within the thesis

1 Introduction

1.1 Introduction to the thesis

Stroke is a leading cause of disability world-wide, up to 65% of stroke survivors do not recover the ability to reach, grasp, and manipulate objects. In the United Kingdom almost £9 billion is spent years on stroke rehabilitation, such as direct costs of therapy and informal care to assist with activities of daily living (ADL). Progress of upper limb rehabilitation is needed to decrease the cost and limit disability after stroke.

Reach-to-grasp is an essential component of ADL's such as dressing and bathing; and reach-to-grasp is often impaired after a stroke. A deeper understanding of the underlying kinematic components that contribute to reach-to-grasp and the kinematic differences between stroke survivors and neurologically intact adults is required. The knowledge of which can be used as targets for improved upper limb interventions.

The primary input from the motor cortex to the muscles of the arm and hand is through the corticospinal pathway. The corticospinal pathway is essential for smooth coordinated arm movement and successful reach-to-grasp. The corticospinal pathway can be assessed using transcranial magnetic stimulation (TMS), which is a non-invasive brain stimulation technique. The knowledge gained from TMS assessment can provide insight into the neural correlates that drive reaching, assess change in corticospinal pathway excitability as a result of a therapeutic intervention, and provide age-matched normative data in neurologically intact adults for comparison to individuals with stroke. This knowledge would be advantageous in the development and assessment of upper limb interventions. To be confident in the results of TMS measures, TMs must be reliable. The test-retest reliability of TMS measures has been focused on investigations in younger adults and in stroke survivors greater than six months after stroke.

There are age-related changes in the central nervous system that may influence TMS measurement and reliability of TMS measurement. The average age of a stroke survivors is 75 years old, normative data in older adults would be beneficial for age-matched comparisons. Similarly, early after stroke there are physiological processes occurring in response to the stroke that are different to later after stroke. The test-retest reliability in young adults and in stroke survivors' later after stroke may not be applicable to older adults and stroke survivors' within the first few months after stroke. Therefore, the test-retest reliability of TMS measures needs to be determined in older adults and in stroke survivors early after stroke.

These research gaps have led to the research studies that comprise the present thesis. The present thesis is constructed of five chapters.

Chapter one is the introduction and background of the literature about stroke, reach-to-grasp, upper limb assessment, neural plasticity, and TMS measurement.

Chapter three is the systematic review investigating the kinematic differences between stroke survivors and neurologically intact adults during reach-to-grasp, and the influence of task requirements on movement kinematics. This chapter includes a short introduction, methods, results, summary of findings, strengths, limitations, and conclusions.

Chapter four is a prospective test-retest reliability study of TMS measures of corticospinal pathway excitability in neurologically intact adults of all ages. This chapter includes a short introduction, methods, results, summary of findings, limitations, strengths, and conclusions.

Chapter five is a prospective test-retest reliability study of TMS measures of corticospinal pathway excitability in stroke survivors within the first three months after stroke. This chapter includes a short introduction, methods, results, summary of findings, strengths, limitations, and conclusions.

Chapter six is the discussion of the three studies in the context of the literature, the strengths and limitations of the thesis, future directions for research, and concluding remarks.

1.2 **Stroke**

Stroke is the third leading cause of disability worldwide (Hankey, 2013). In the United Kingdom (UK) cardiovascular disease including stroke is the largest cause of death with approximately 152,000 new stroke per year (Stroke Association, 2013). Stroke is damage or death of brain tissue due to an absence of oxygenated blood flow (WHO, 2015). There are two types of stroke; the first is an ischemic stroke in which a blood clot in an artery of the brain interrupts the flow of oxygenated blood to the surrounding brain tissue. The second, is a haemorrhagic stroke in which blood vessel walls become thin and weak, eventually rupturing causing bleeding in and around the brain tissue which leads to swelling within and around the brain tissue (WHO 2015). The swelling restricts blood flow leading to an absence of oxygenated blood flow to the surrounding brain tissue. The absence of oxygenated blood to the brain tissue leads to tissue death, consequently, the associated function of the brain tissue (brain area) can become lost or impaired (Witte et al., 2000). For example, a stroke in the area of the motor cortex served by the middle cerebral artery may lead to weakness of the upper or lower limb, trunk or face. The weakness may impair the use of the upper or lower limb for movement such as reaching and walking, the trunk for stability, and the facial muscles for speaking and swallowing. Risk factors associated with stroke include age, in which

the incidence increases from about age 55 and continues to increase, hypertension (high blood pressure) weakening of the artery walls, hyperlipidaemia leading to build up of plaque formation in blood vessel walls, smoking, increased body mass index (BMI), and diabetes (Xanthakis et al., 2014). Of these risk factors, age is the only non-modifiable risk factor.

Improved health care is contributing to people living longer. It is estimated that in the UK in 2009 almost £ 9 billion were spent on stroke care. Of the £ 9 billion, about 50% is in direct costs, 27% in indirect costs, and 24 % in informal care (Saka et al., 2009). Direct costs include hospitalization and rehabilitation which accounts for about £ 4.4 billion about 5.5% of the total National Health System (NHS) expenditure; indirect costs are income loss and social benefit payments (Saka et al., 2009). In addition to people living longer and having more strokes the survival rate after stroke has also improved.

Survival after stroke has increased in part because of improved prevention programs and improved health services for acute stroke care. For example, from 1990 to 2010 mortality from stroke decreased about 46% (Feigin et al., 2014). Improved health services and the advent of thrombolysis has been associated with decreased mortality and decreased disability after stroke (Fonarow et al., 2014, Wardlaw et al., 2012). Thrombolysis is intravenous administration of tissue plasminogen activator which is a drug that assists in dissolving or breaking up the blood clot that is contributing to ischemic stroke. As the blood clot dissolves, cerebral blood flow can return to the area thus giving the surrounding tissue an opportunity to receive oxygen and prevent tissue death. Similar to a surface wound, the neural tissue in the centre of the stroke dies as this is the area of the brain that has had greatest loss of blood supply and therefore oxygen. The surrounding brain tissue, called the penumbra, can be lost due to cell death or can undergo revascularisation through return of blood flow, which may facilitate improved recovery (Witte et al., 2000). Thrombolysis is time sensitive, the sooner stroke symptoms are noticed and medical care is received, the better the outcome (Fonarow et al., 2014, Wardlaw et al., 2012). Current guidelines state that thrombolysis needs to be administered within three hours of onset of symptoms for all patients and can be administered up to six hours from symptom onset on an individual basis (Party, 2012). For stroke survivors there is an associated disability despite participation in rehabilitation (Kwakkel et al., 2003, Lai et al., 2002, Lawrence et al., 2001).

1.3 **Stroke and upper limb disability**

Of stroke survivors, up to 77% report upper limb motor deficits (Lawrence et al., 2001). Upper limb motor deficits can impair a stroke survivor's ability to use their upper limb for ADL's such as eating and dressing. Approximately 65% of stroke survivors do not incorporate their involved upper limb into ADL's (Dobkin, 2005). Despite participation in

rehabilitation, stroke survivors continue to demonstrate upper limb deficits (Kwakkel et al., 2003, Langhorne et al., 2011). For example, it was estimated that in a group of 102 participants with a middle cerebral artery stroke 62% did not regain 'some' dexterity of their more affected upper limb (Kwakkel et al., 2003). 'Some' dexterity was measured by a score of ten or more on the Action Research Arm Test (ARAT) indicating difficulty or inability to reach, grasp, or transporting objects at six months after stroke. Stroke survivors with mild motor deficits reported lower levels of hand function, decreased independence with ADL's, and overall decreased physical function (assessed by the Stroke Impact Scale) compared to community dwelling older adults (Lai et al., 2002). Additionally, stroke survivors with mild motor deficits also reported decreased real-world arm use (Lum et al., 2009). Thus, a majority of survivors are living with some level of disability; sub-optimal recovery can have a psychological impact on the stroke survivor and their family.

Decreased independence with ADL's can lead to increased reliance on others for assistance in basic activities. There are approximately 200,000 stroke survivors that require assistance from professional carers or family members to complete activities of daily living (Di Carlo, 2009, Saka et al., 2009). Of the £9 billion spent on stroke care in the UK, about 24% is in informal costs for professional carers or family members (Saka et al., 2009). Assistance from family members or partners can change the dynamic of the relationship and put additional stress on relationships. Assistance for mobility may contribute to stroke survivors not leaving their home; this may lead to social isolation and limited participation in activities they enjoy, which can subsequently lead to depression (Mayo et al., 2002). Discharge to a nursing home or care home could further isolate the stroke survivors from their family, friends, and activities. A recent systematic review found that approximately 31% (95% CI of 28-35%) of stroke survivors suffer from depression (Hackett and Pickles, 2014), and there is evidence that depression can have a negative effect on functional outcomes (Ahn et al., 2015). Improved functional outcomes after stroke may contribute to better upper limb motor function, independence with ADL's (decreased reliance on others for help), and decreased cost of rehabilitation through more efficient treatment. Improved upper limb outcomes may be accomplished through improved targeted rehabilitation interventions.

A recent systematic review evaluated the effectiveness of different upper limb therapies after stroke. The findings were that there was not one optimal therapy (Langhorne et al., 2009). This may be because of heterogeneous presentation and recovery after stroke. As all stroke survivors have individual movement deficits, it may be more beneficial to have more individualised, precise, targeted therapies aimed at specific movement dysfunctions and specific presentations of impairments.

To develop more precise and targeted interventions, there needs to be a deeper understanding of the underlying movement components and neural control of movement within normal movement control in neurologically intact adults, and the deficits of movement in stroke survivors. This knowledge may provide more objective and detailed knowledge of movement characteristics from which it may be determined where interventions should be targeted. A starting point for this is a deeper understanding of the kinematics of reach-to-grasp.

1.4 Reach-to-grasp

Reach-to-grasp is an essential component of upper limb movement and part of almost all ADL's, such as reaching for a cup, putting on a shirt, or brushing teeth. We use our upper limbs for functional activities throughout the day. A study by Rand and Eng, (2012) assessed the frequency of upper limb use in stroke survivors and age-matched healthy adults through wearing of wrist accelerometers. The healthy older adults used their right hand on average 184,761 (131,523 to 241,819) times a day, and their left hand on average 159,698 (107,826 to 217,489) times a day. In contrast, the stroke survivors at the start of a rehabilitation program used their paretic hand on average 37,734 (18,167 to 84,238) times and their non-paretic hand 147,500 (90,477 to 224,835) times a day (Rand and Eng, 2012). After completion of the rehabilitation program the stroke survivors used their paretic hand 41,541 (19,300 to 105,590) times and their non-paretic hand 164,185 (95,287 to 212,920) times a day. Stroke survivors used both their paretic and non-paretic upper limbs 78% and 12% less than control participants (right hand) respectively (Rand and Eng, 2012). Decreased use of the upper limb for functional activities is related to impaired motor function and associated with poorer quality of life (Nichols-Larsen et al., 2005). Reaching is the target of many upper limb therapies such as repetitive task practice (Michaelsen et al., 2006), functional strength training (Cooke et al., 2010b, Donaldson et al., 2009), and constraint induced movement therapy (Wolf et al., 2006).

Successful reach-to-grasp requires complex interaction between mobility and stability. This coordination of movement is accomplished through simultaneous activation of the musculoskeletal and nervous systems (McCrea et al., 2002, van Vliet et al., 2013).

The musculoskeletal system is comprised of the muscles, tendons, bones, cartilage and ligaments and provides the underlying muscle power and range of motion that contributes to the biomechanics of movement (McCrea et al., 2002). For neurologically intact individuals reaching within arm's reach requires recruitment of the shoulder, elbow/forearm, wrist, and hand. Whereas, reaching outside arm's length requires the addition of the trunk and hip joints (Michaelsen et al., 2001). During reach-to-grasp the muscles provide simultaneous mobility and stability across the joints of the arm and hand

to transport the hand to the desired location (Liu et al., 2013). For example, the shoulder and elbow are active to transport the arm to the cupboard while the wrist and hand are stable. When the hand is at the cupboard the shoulder and elbow are stable to assist the wrist to extend and position the hand at the desired object. When the hand is at the object the hand and wrist are active for object manipulation. The complex coordination of muscle activity that contributes to performance of movement is directed by the nervous system.

The nervous system is comprised of the central nervous system (CNS) including the brain, spinal cord, and cranial nerves, and peripheral nervous system (PNS) including peripheral nerves. The nervous system provides "how to" for movement. For example generating the motor plan, executing the motor plan via the neural pathways which activate the muscles, and direct movement adjustments based on peripheral feedback. (McCrea et al., 2002).

1.4.1 **Neural control of reach to grasp**

Successful reach-to-grasp is accomplished by an ongoing feedback loop from the peripheral nervous system to the central nervous system directing movement adjustments to achieve the task goal. The key connection between the nervous system and voluntary upper limb movement is the corticospinal pathway. The corticospinal pathway is integral to the descending portion of the feedback loop, smooth coordinated upper limb movement, and successful reach-to-grasp (Butler and Wolf, 2007, Shumway-Cook and Woollacott, 2007). The corticospinal pathway originates in the anterior region of the motor cortex of the brain and terminates with peripheral nerves that innervate the muscles of the upper limb, trunk and lower limbs Figure 1. The corticospinal pathway receives inputs from the primary motor cortex, supplementary motor cortex, and premotor cortex (dorsal and ventral) (Sharma and Cohen, 2012). The corticospinal pathway has monosynaptic connections with alpha motor neurons, and polysynaptic connections to gamma motor neurons and spinal neurons (Shumway-Cook and Woollacott, 2007).

A schematic detailing the feedback loop can be found in Figure 2. To describe this process the example of grasping a cup will be used. Briefly, a motor plan to advance the arm and hand towards the cup is generated in the motor cortex based on previous experience, sensory feedback, and the environment. The brain areas involved in movement planning prior to limb movement are the premotor cortex, insula, pre-supplementary motor area, superior temporal gyrus, parietal area, and parieto-occipital cortex (Glover et al., 2012). The neural impulses generated by the motor plan are carried out via the corticospinal pathway to activate the muscles of the arm and hand (Shumway-Cook and Woollacott, 2007). The activated muscles transport the limb

towards the object; during limb transport peripheral feedback from the environment (external), and internal feedback such as movement speed, joint position, and somatosensory information, is sent back to the sensorimotor area of the brain. The brain areas involved in control of movement are the sensorimotor cortex, cerebellum, supramarginal gyrus, and the superior parietal lobule (Glover et al., 2012). These brain areas synthesize the peripheral feedback and modify the motor plan. The new modified motor plan is again executed through the corticospinal pathway which activates the muscles of the arm and hand to move the hand towards the cup. This feedback loop is continuous until the goal is achieved, successful grasp of the cup.

The feedback loop and process of reach-to-grasp in neurologically intact individuals is seamless and unconscious. However, for a stroke survivor, reach-to-grasp may be challenging and for some impossible. After a stroke there can be a disruption in any part of the feedback loop which will lead to impaired reach-to-grasp. For example, a stroke affecting the primary motor cortex and the corticospinal pathway can lead to the neural impulses traveling via an alternative pathway to the muscle that is less efficient. Alternatively, if there is a stroke in a brain area that has connections to the motor cortex such as the cerebellum, may impair the processing of peripheral feedback, which potentially leads to decreased control of movement and imprecision.

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Figure 1 - Corticsospinal Pathway

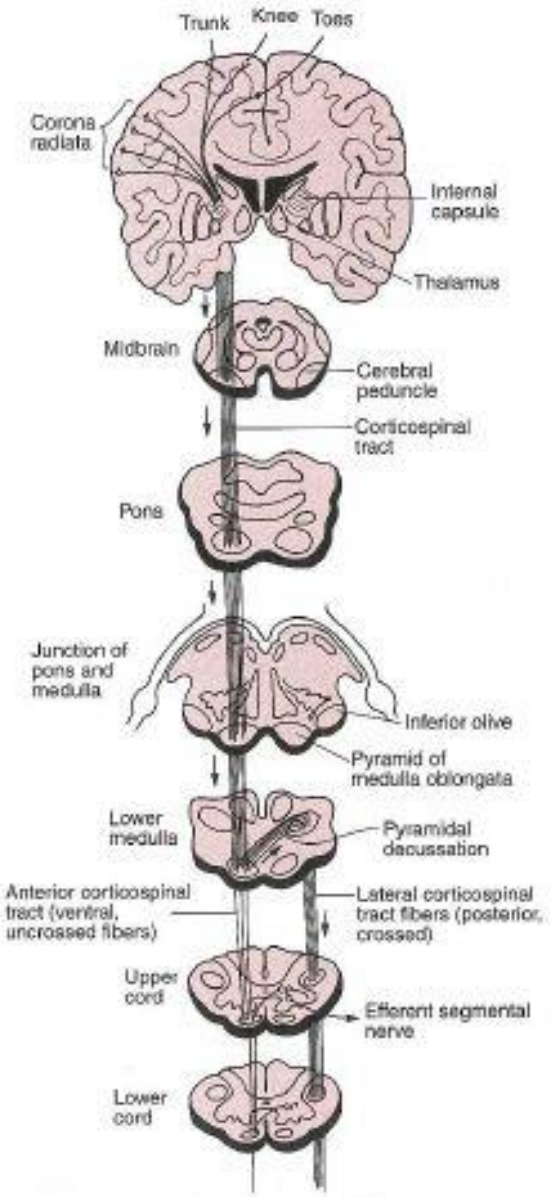


FIGURE 3.14 Pyramidal (corticospinal) tract.

Figure 1 - Diagram of the corticospinal pathway; the corticospinal pathway originates in the motor cortex, travels through the midbrain, pons, and medulla where most fibres cross contralaterally to descend though the spinal cord. The neurons then synapse with spinal motor neurons, peripheral neurons and terminate at the muscles of the upper limbs, lower limbs and trunk. (Figure from Shumway-Cook and Woollcott, 2007)

Figure 2 - Schematic detailing the feedback loop during reach-to-grasp

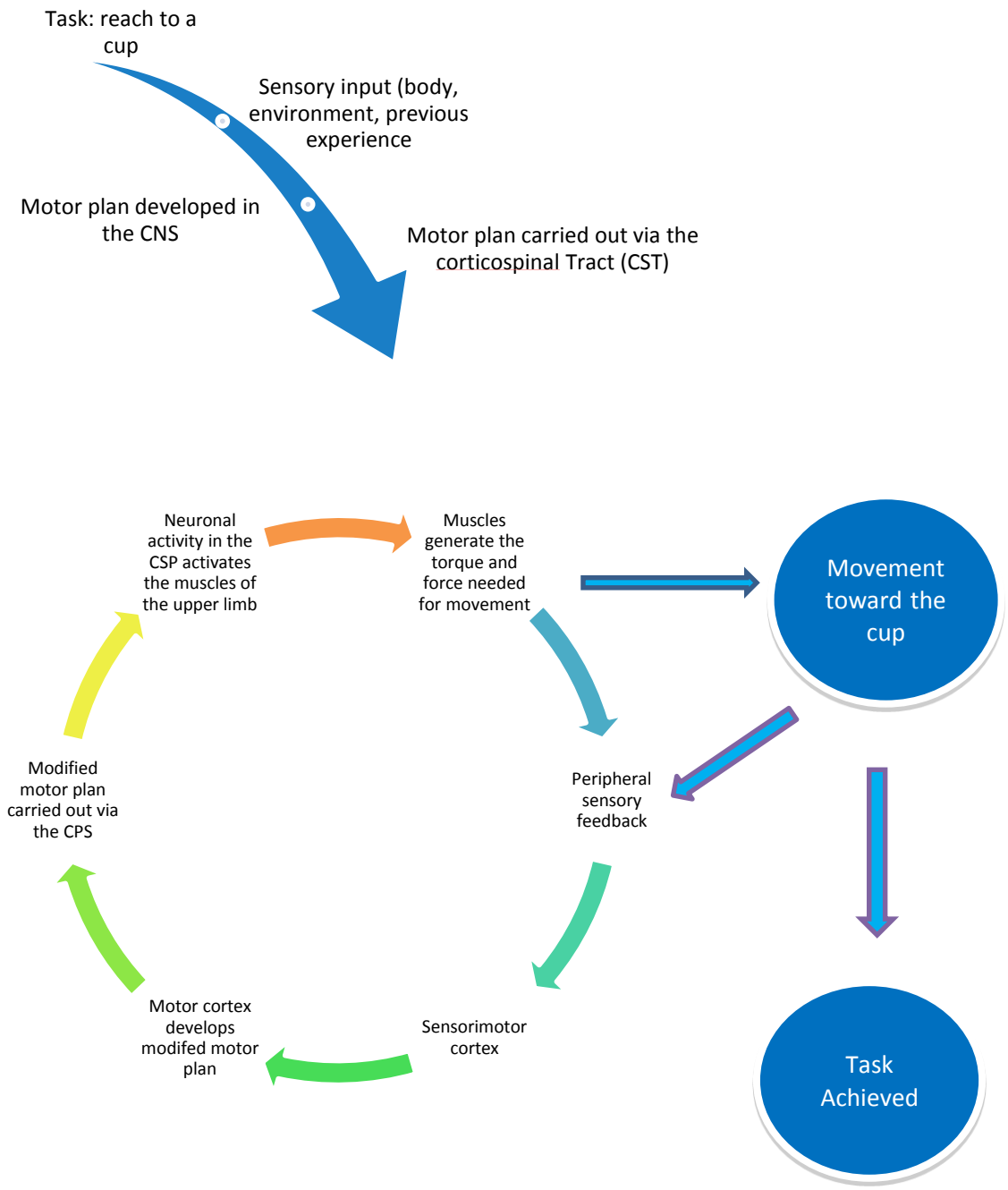


Figure 2- Schematic of neural control of reach-to-grasp. The motor plan is developed in the motor cortex, the neural impulses are carried via the corticospinal pathway to activate the muscles of the arm and hand. The active muscles transport the arm and hand towards the object, simultaneously there is ongoing peripheral feedback being sent back to the sensorimotor cortex. The sensorimotor cortex updates the motor plan based on this feedback; new neural impulses are sent via the corticospinal pathway to activate the muscles of the arm and hand. This loop continues until the task goal is achieved.

To better understand deficits of movement during reach-to-grasp in stroke survivors, there needs to be a firm knowledge base of the range of normal movement during reach-to-grasp in neurologically intact adults. The differences in movement between stroke survivors and neurologically intact individuals can then be compared.

1.5 Assessment of reach-to-grasp

There are different instruments available to assess movement during reach-to-grasp including observational assessment, kinematic assessment, and electromyography (EMG) assessment. Each provides different knowledge of movement and will be discussed individually.

1.5.1 Clinical observational assessment

Clinical measures are useful to determine if an individual can or cannot complete specific tasks, assist in clinical decision making (interventions), and monitor progress. However, observational clinical measures of upper limb motor ability have low sensitivity (Carpinella et al., 2006, Nowak, 2008), and are not able to assess or monitor change in individuals with mild motor deficits (Platz et al., 1999). Clinical observational measures of upper limb movement such as the ARAT or Wolf Motor Function Test (WMFT) both include reach-to-grasp tasks. The ARAT includes tasks of reach-to-grasp and transport of blocks, tubes, and cups, as well as fine motor activities of pinching marbles and ball bearings. The ARAT is scored by the therapist observing arm and hand movement during the tasks; scores range from 0 to 3; 0 = cannot perform and 3 = performs test normally (Lang et al., 2006, Lyle, 1981, Nijland et al., 2010). Similarly, the WMFT assesses upper limb function, dexterity, and strength through tasks such as reach-to-grasp of everyday objects such as a can, pencil, paperclip, and checkers. The WMFT is scored by the therapist through movement observation, the scores range from 0-5, 0="does not attempt with the involved arm" to 5= "arm does participate, movement appears to be normal" (Wolf et al., 2001). Neuro-biomechanical assessment of movement such as kinematic assessment and electromyography assessment may provide more objective and sensitive measures of movement.

1.5.2 Neuro-biomechanical assessment

Neuro-biomechanical assessments of movement and of reach-to-grasp include kinematic and electromyography assessment. Firstly, kinematic assessment provides objective knowledge of movement control (McCrea et al., 2002) and can determine the underlying kinematic mechanisms of both movement and deficit of movement (Platz et al., 1999) such as the joint motion, velocity, smoothness, and trajectory. Secondly, kinematic assessment is reliable, sensitive to monitor change, and can distinguish between proximal and distal dysfunction, for example transport versus grasp respectively (Lum et al., 2009, Nowak, 2008, Platz et al., 1999, Caimmi et al., 2008). Finally, kinematic

assessment can identify movement deficits in stroke survivors with mild upper limb motor impairment, who when observed have movement patterns similar to healthy controls (Platz et al 1999).

EMG is the assessment of muscle activity, muscle activation patterns, and muscle agonist and antagonist pairs. EMG can provide "a description of the activation patterns which constitute the interface between the central nervous system and the biomechanics of the arm" (Flanders et al., 1996). EMG can be used during isometric muscle contractions to evaluate muscle activity and EMG can be used during functional activities such as walking or reach-to-grasp. EMG used during functional activities can provide knowledge of muscle activation, sequence of activation, muscles agonists and antagonists to better understand how the CNS and musculoskeletal system work together to complete a specific activity.

Previous research has demonstrated that in neurologically intact adults, reach-to grasp movements are smooth, reproducible (Cirstea and Levin, 2000, Micera et al., 2005), demonstrate trunk recruitment only for objects outside arm's length (Levin et al., 2002, Michaelsen et al., 2001), exhibit consistent muscle activation patterns (Vandenberghe et al., 2010), and have coordinated reach-to-grasp (van Vliet et al., 2013). However, stroke survivors movements are slower (van Vliet and Sheridan, 2007), demonstrate trunk recruitment to reach within and outside arm's length (Levin et al., 2002), exhibit segmented movement (Cirstea et al., 2003), inconsistent recruitment of muscles (Massie et al., 2012, McCrea et al., 2005), and impaired coordination of reach-to-grasp (van Vliet et al., 2013). A deeper understanding of movement control related to specific task restraints such as object placement may make the interpretation of stroke survivors' movement control more meaningful and assist in development of more precise targeted interventions which are aimed at underlying movement control. The development of more precise interventions may contribute to more efficient rehabilitation, improved upper limb outcomes, and decreased assistance for ADL's. This would benefit stroke survivors though decreased disability, improved independence as well as would benefit the NHS through decreased cost of stroke services (direct, indirect, and informal costs).

The development of more precise interventions can be achieved by combining different assessment tools to provide a deeper understanding of kinematic movement control during reach-to-grasp; through a better understanding of the interaction between the nervous and musculoskeletal systems. The evaluation of the interaction between upper limb movement and specific interventions and the neural correlates of reach-to grasp can be accomplished through neuroimaging and non-invasive brain stimulation technology which can indirectly assess neural plasticity, which is the brains ability to adapt and form new connections in response to motor learning.

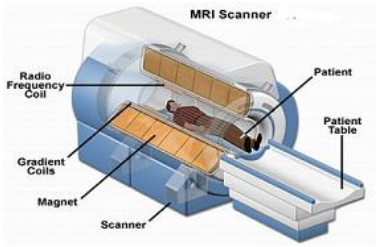
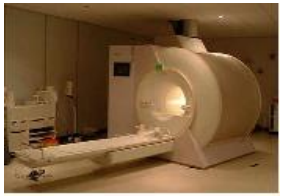
1.6 Neuroimaging and non-invasive brain stimulation

Research in human neural plasticity is possible due to development of technology that can assess the central nervous system. There are different technologies that can assess neuroplasticity such as functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), positron-emission tomography (PET), magneto-encephalography (MEG), and transcranial magnetic stimulation (TMS). Each neuroimaging technology has benefits and limitations of its use and these are outlined in Table 2.

Functional magnetic resonance imaging or fMRI can assess brain areas of activation during a functional task such as finger tapping. A brain map of active areas is created by using an imaging technique called blood oxygen level-dependent imaging (BOLD signal), that map the active brain areas during a specific functional task such as finger tapping (Chen 2010). The active brain areas during the finger tapping task utilise increased oxygen, thus there is increased blood flow to those regions; and the active regions appear a different colour on the fMRI scan. The brain map derived from fMRI is useful to determine what brain areas are active during specific tasks, and to assess neural plasticity by evaluating how the areas of activation change over time following a rehabilitation intervention. There are limitations to fMRI: it is not portable, it is expensive, there is a confined environment within the scanner (claustrophobia), individuals with implanted metal cannot participate, there can be artefact from head movement, and the fMRI output is unable to distinguish if the brain activation is inhibitory or facilitatory to function (Chen et al., 2010, Dimyan and Cohen, 2011, Schaechter, 2004).

Diffusion tensor imaging, DTI, examines the microstructure of brain structures through the evaluation of diffusion of water within the brain tissue and neural pathways (Chen et al., 2010). Evaluation of the microstructures can determine the integrity of the neural pathways and motor tracts such as the corticospinal pathway that may be compromised by the stroke. DTI can also evaluate neural plasticity by the change in the integrity of the pathway following a rehabilitation intervention. The limitations of DTI are similar to those of fMRI.

Table 2Technology of Assessment of Neural Plasticity

Technology	How it works	Use	Benefits	Limitations
fMRI (functional magnetic resonance imaging) 	-Develops a brain map of active areas by mapping blood flow using blood oxygen level-dependent imaging (BOLD) during a chosen functional task such as finger tapping	- Determine what brain areas are active during a specific functional task - Assess neural plasticity by how the areas of activation change following a rehabilitation intervention over time	-Able to determine all brain areas that are active during a specific task (what areas work together) -3D image of the brain and active areas -Good spatial and temporal resolution, absence of ionizing radiation, wide availability (compared to PET scan)	-Not portable -Confined environment in the scanner (claustrophobia) -Cannot participate if the person has implanted metal -Acoustic noise -Artifact from head movement -Less sensitive than PET
DTI (diffusion tensor imaging) 	-Examines the microstructure of brain structures via diffusion of water in brain tissue and neural pathways	-Determine the integrity of neural pathways that may be compromised by stroke -Assess neural plasticity following a rehabilitation intervention	-Assess the integrity of white matter tracts following stroke	-Not portable -Confined environment in the scanner (claustrophobia) -Cannot participate if person has implanted metal
MEG (magnetoencephalography) 	-Records magnetic fields that are produced by naturally occurring electrical currents in the brain using sensitive magnetometers.	-Localising brain regions affected by pathology -Determine the function of brain areas during a specific task -Neurofeedback -Determine sensorimotor area reshaping related to therapeutic intervention	-Brain mapping of re-organisation -Determine brain areas that are active during a specific functional task -High temporal resolution (1 millisecond))	- Not portable - Cannot participate if person has implanted metal - Poor spatial resolution compared to fMRI

Technology	How it works	Use	Benefits	Limitations
TMS (Transcranial magnetic stimulation) 	-A magnetic impulse induces an electrical current in brain tissue, this indirectly stimulates the corticospinal pathway; the response is measured with EMG at the muscles of the arm and hand	-Assess integrity and excitability of the corticospinal pathway -Assess neural plasticity following a rehabilitation intervention	-Can be used during active muscle contraction or at rest which is beneficial for those individual with hemiplegia -Portable -Motor area mapping –Determine excitability and integrity of the corticospinal pathway	-Cannot participate if a person has implanted metal, seizures, large area of brain damage, a cardiac pacemaker/defibrillator, or hydrocephalus shunt.
PET (Positron emission tomography) 	-Develop a brain map by measuring blood flow or metabolic changes to the brain areas that are active during a specific functional task -The blood flow and metabolic changes are determined by administering a radioactive tracer	-Determine what areas of the brain are active during a specific task -Monitor change in activation/neural plasticity after a rehabilitation intervention	-More physiologic room for individuals to complete limb movement or for additional monitoring of movement such as EMG -No magnetic fields used, can participate if you have implanted metal	-Requires intravenous injection of a radioactive tracer substance therefore is invasive

Table 2 Describes the neuroimaging techniques commonly used in rehabilitation research including fMRI, DTI, MEG, TMS, and PET their uses, benefits, and limitations. References: (Chen et al., 2010, Schaechter, 2004).

PET assessed blood flow changes or metabolic changes to derive a brain map of active brain areas during a functional task such as finger tapping. A radioactive tracer is induced to the body via an intravenous injection. The tracer is then taken up by the blood stream and travels throughout the body and the brain (Chen et al., 2010, Schaechter, 2004). Similar to fMRI, during the functional task the active brain areas will require increased oxygen and blood flow, thus increased tracer in the active areas can be tracked and mapped. The brain map describes what areas of the brain are active during specific tasks and can assess neural plasticity through changes in the brain map after a rehabilitation intervention. Limitations to PET scans are that they are invasive due to the intravenous injection of the radioactive tracer, it is not portable, and similarly to fMRI PET is unable to determine if the brain activation seen is facilitatory or inhibitory (Chen 2010, Dimyan and Cohen 2011).

MEG uses magnetic fields to record natural occurring electrical currents in the brain through the use of sensitive magnomoters during a functional activity such as finger tapping (Schaechter, 2004). MEG is able to localise brain regions affected by the stroke, determine the function of brain areas during a specific task, provide neurofeedback, and determine sensorimotor reshaping related to rehabilitation interventions. The limitations of MEG are that it is not portable, there is poor spatial resolution when compared to fMRI, and individuals cannot participate if they have implanted metal (Schaechter, 2004).

1.6.1 **Non-invasive brain stimulation**

TMS involves a magnetic impulse over the motor cortex which induces an electrical field in the brain tissue below activating the neurons within the corticospinal pathway, the response is a motor evoked potential, MEP (Wassermann et al., 2008, Butler and Wolf, 2007, Schaechter, 2004). Evaluation of the MEP can assess the integrity or excitability of the corticospinal pathway and can be used to assess neural plasticity following a rehabilitation intervention. The limitations of TMS are that individuals with implanted metal, a seizure disorder, brain or spine surgery, or implanted devices such as a cardiac pacemaker, hydrocephalus shunt, or drug infusion pump cannot participate (Rossi et al., 2009). TMS can be completed during active muscle contraction or at rest, allowing individuals without active movement to participate.

In summary, fMRI, PET, and DTI are assessments within enclosed spaces thus those with claustrophobia could not participate, are not portable, and cannot distinguish between inhibitory and facilitatory activation. Individuals with implanted metal can only participate in PET scanning. TMS has additional contraindications including those individuals who have a seizure disorder, implanted devices, or brain and spine surgery cannot participate. The length of time it takes to complete assessments is also a factor, fMRI, PET, MEG and EEG require lengthy testing, which is time away from rehabilitation.

Transcranial magnetic stimulation (TMS) is advantageous in both assessing neural plasticity and exploring the interaction between the nervous and musculoskeletal systems. TMS is portable (can be used in the hospital and other clinical settings), takes a reasonable amount of time to complete, can be completed during active muscle contraction or with the muscle at rest allowing assessment of individuals with severe hemiparesis, and the participant is never enclosed (those with claustrophobia are able to participate) (Wassermann et al., 2008, Schaechter, 2004). A limitation of TMS is that people with implanted metal cannot participate; however people with implanted metal would not be able to participate in fMRI, MEG, or DTI as these assessments also utilise magnetic fields TMS has been used with neurologically intact populations (Christie et al., 2007, Koski et al., 2005, Malcolm et al., 2006) and with clinical populations such as stroke survivors to investigate the integrity of the corticospinal pathway, and neural plasticity (Park et al., 2004, Brouwer and Schryburt-Brown, 2006, Koski et al., 2004), multiple sclerosis to investigate fatigue (Liepert et al., 2005), Parkinson's Disease to assess intra-cortical connections (Bareš et al., 2003), and in the diagnosis of ALS (Pouget et al., 2000).

1.7 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation is non-invasive brain stimulation technique based on the principles of electromagnetism, such that TMS coil produces a magnetic field, the changing magnetic field in the coil then induces a flow of electric current in the brain tissue below activating the neurons (Wassermann et al., 2008, Rossini and Rossi, 2007, Butler and Wolf, 2007) demonstrated in Figure 3. When the magnetic impulse occurs over the motor cortex, the neurons within in the corticospinal pathway are activated through depolarisation; the response is a brief natural muscle contraction. The natural muscle contraction can be measured using EMG at the target muscle of interest for example a muscle in the upper limb. The muscle response is a motor evoked potential, MEP.

Figure 3 - Schematic of TMS

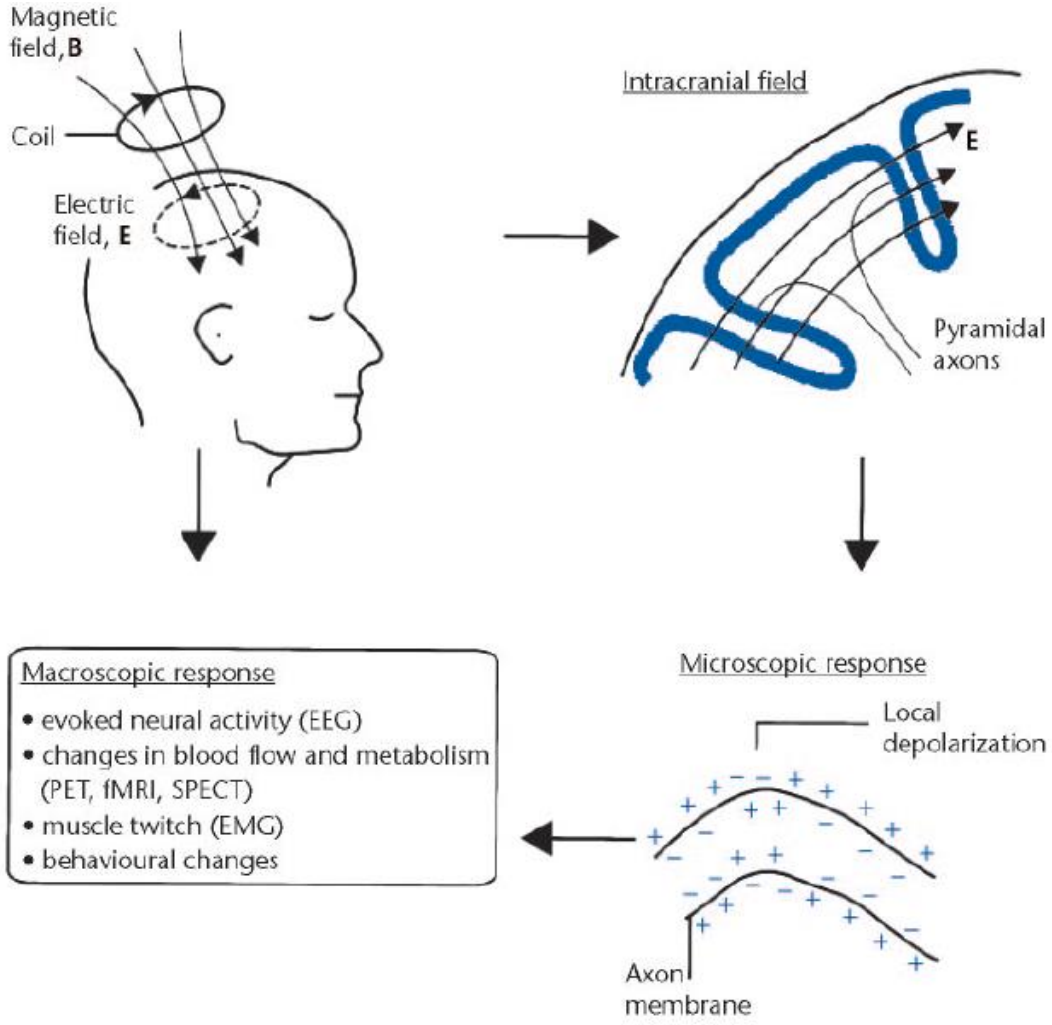


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Figure 3 - TMS; magnetic impulse over the scalp induces an electrical current in the brain tissue below, specifically the corticospinal pathway when the coil is over the motor cortex. The electrical current in the brain tissue leads to axonal depolarisation and neuronal firing. Neuronal firing in the corticospinal pathway activates the muscles of the upper or lower limb resulting in a muscle twitch

or contraction which can be measured with surface electromyography. (Figure from Butler and Wolf 2007).

There are different types of TMS such as single pulse TMS, repetitive TMS (rTMS) encompassing theta burst stimulation (TBS), paired pulse TMS (ppTMS), and paired associated stimulation (PAS). These different types of TMS allow us to measure and investigate different properties of the corticospinal pathway and connections with the motor cortex.

1.7.1 **Types of transcranial magnetic stimulation**

The different types of TMS are used to investigate the excitability of the corticospinal pathway (single pulse TMS), can increase or decrease excitability of neurons or brain areas (rTMS, TBS, ppTMS), and can be used to induce neural plastic changes within a brain area such as the motor cortex (PAS).

Firstly, single pulse TMS involves a single magnetic impulse at a given time and is used to evaluate the excitability of the corticospinal pathway. Evaluation of the excitability of the corticospinal pathway allows researchers to examine physiology of movement, neural plasticity, and derive motor maps of specific muscle representations (Rossini et al., 2010, Wassermann et al., 2008, Mishra et al., 2011). Assessment of the change in measurement of the excitability of the corticospinal pathway before and after an intervention is an indirect measure of neural-plasticity within the motor cortex and corticospinal pathway (Koski et al., 2004, Park et al., 2004, Wolf et al., 2006). Within single pulse TMS there are different elements of the MEP response that can be measured. Each element provides different information about the connection between the brain and the muscles. These elements will be discussed in detail in the following section 1.7.2.

Secondly, rTMS delivers repetitive trains of TMS pulses in quick succession at a given time. Low frequency rTMS < 1 Hz can induce long term depression decreasing intracellular communication, whereas high frequency rTMS > 1 Hz can induce long term potentiation increasing intracellular communication (Mishra et al., 2011). Repetitive TMS can be used to either increase or decrease excitability of a specific brain area. For example, excitatory rTMS given over the motor cortex has been shown to improve motor function, whereas inhibitory rTMS can decrease motor function. Repetitive TMS has been used in this way in healthy people to induce “virtual lesions” to probe how motor function changes in relation to specific brain areas (Narayana et al., 2014, Vollmer et al., 2015). Repetitive TMS has also been used in stroke survivors; excitatory rTMS has been administered over the lesioned hemisphere to increase excitability and prime the motor system before a motor intervention. Alternatively, inhibitory rTMS can be administered over the non-lesioned hemisphere to decrease excitability of the non-lesioned hemisphere which is thought to facilitate increased neuronal recruitment of the lesioned hemisphere (Fregni et al., 2006, Boggio et al., 2006). TBS is a type of rTMS that

consists of short bursts of stimulation at about 50-100 Hz and repeated at a frequency of 5Hz. This form of stimulation is thought to resemble neuronal firing in the hippocampus of rats (Mishra et al., 2011, Rossini et al., 2010), and being used to increase and decrease excitability of specific brain regions.

Thirdly, ppTMS involves two stimuli given in a specific sequence; first a sub threshold stimulus is delivered followed by a suprathreshold stimulus. The time interval between stimuli has different effects on cortical tissue. A short inter-stimulus interval such as 1-4 milliseconds (ms) can induce intracortical inhibition, whereas a longer inter-stimulus stimulus interval of 7-12 ms can induce intracortical facilitation (Mishra et al., 2011, Rossini et al., 2010). Paired pulse TMS can be used to investigate excitatory and inhibitory facilitation between the right and left hemispheres in neurologically intact individuals as well as in those with neurological disease (Casadio et al., 2009, Peinemann et al., 2001).

Finally, PAS can induce neural plastic changes in the sensorimotor cortex through combining electrical stimulation of a peripheral nerve with a magnetic pulse over the scalp. This type of stimulation can induce plasticity based on the interval between stimuli. If the peripheral stimulus arrives at the motor cortex before the magnetic stimulus it can induce cortical excitability and thus facilitate neural plasticity (Carson and Kennedy, 2013, Rossini et al., 2010).

The different types of TMS provide valuable knowledge to better understand the connection between the brain and muscles of the upper limb, induce and explore the relationship between brain areas and motor function, and to facilitate neural plasticity. The focus of this thesis is on single pulse TMS and its measurement of the MEP.

1.7.2 **Motor evoked potential**

As previously mentioned the natural response to single pulse TMS given over the motor cortex is a brief natural muscle contraction, a MEP that is measured using EMG at the target muscle of investigation. The transient electrical field created by the magnetic field (impulse) causes the neurons to depolarise. The neurons depolarise through calcium and sodium ions flooding the axonal membrane and potassium ions exiting the membrane. The increase of calcium and sodium within the axonal membrane facilitates depolarisation of the axons which leads to an action potential and propagation. Depolarisation spreads to connecting axons resulting in a natural muscle contraction, MEP (Wassermann et al., 2008, Butler and Wolf, 2007). There are different aspects or elements of the MEP that can be investigated such as MEP amplitude, MEP latency, silent period, motor threshold, and a recruitment curve. Each element provides different information about the connection between the brain and the muscles, and is sensitive to

measure neural plasticity. The individual MEP elements are summarised in Table 3 and each element will be discussed individually.

Firstly, MEP amplitude is a measure of the excitability of motor neurons in the corticospinal pathway that are activated by the TMS stimulus (Rossini and Rossi, 2007, Chen, 2000). Amplitude measured during a muscle contraction is greater than when measured at rest. During muscle contraction the corticospinal pathway is pre-activated though the activation of spinal neurons, the TMS stimulus is thus superimposed on an active system resulting in a larger amplitude response (Rossini and Rossi, 2007).

Secondly, MEP latency is a measure of conduction time which is the time from TMS stimulus until the onset of the MEP on the EMG recording (Rossini et al., 2010, Rossini and Rossi, 2007). The latency can be influenced by the diameter of the motor fibre, myelination, number of connecting impulses, current direction, and background muscle contraction during data collection (Rossini et al., 2010).

Thirdly, the silent period is the period of absent muscle activity on EMG after the TMS stimulus. The silent period is a measure of intra-cortical integrity; the first part is thought to be due to spinal mechanisms, whereas the second part is thought to be due to cortical mechanisms (Chen, 2000, Liu and Au-Yeung, 2014, Wassermann et al., 2008).

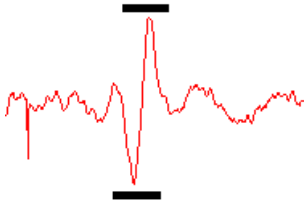
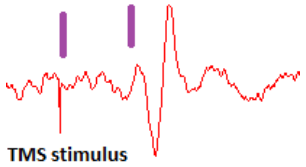
Fourthly, the motor threshold is the lowest TMS stimulus measured as the percentage of stimulator output required to elicit a MEP. Motor threshold is a measure of excitability of the membrane that surrounds the neurons in the corticospinal pathway (Chen, 2000), and is different for each muscle of the upper limb. The motor threshold is higher for proximal muscles and lower for distal muscles of the upper limb, which is thought to be related to mono-synaptic (corticospinal) connection with hand muscles whereas, the proximal muscles exhibit greater inter-neuron connections (Turton et al., 1996). Muscle contraction during TMS lowers the motor threshold, as the corticospinal system is pre-activated, the neurons need a lower magnetic impulse or stimulus to yield a response (Chen, 2000, Rossini et al., 2010).

Finally, another way to investigate the corticospinal pathway is to systematically collect MEP's with increasing TMS stimulus; this is called a recruitment curve, stimulus response curve, or input-output curve. With an increasing TMS stimulus there is an increase in MEP amplitude; the recruitment curve can measure neurons that are less excitable and farther from the centre of TMS activation (Massie and Malcolm, 2013, Chen, 2000). The slope or steepness of the curve is related to the strength of the intracortical and corticospinal connections with the target muscle (Liu and Au-Yeung, 2014). Change in the slope of the curve over time or after an upper limb intervention can be due to changes in the distribution of the excitability of the corticospinal pathway or changes within the spatial distribution of stimulated neurons (Siebner and Rothwell,

2003). Thus, the slope of the recruitment curve has been used as an indirect measure of neural plasticity.

Assessment of the motor evoked potential has provided researchers and clinicians with growing evidence of how the human brain responds to learning, and undergoes neural plasticity.

Table 3- Motor Evoked Potential Elements

MEP Element	Definition and what it measures	Method of data collection
MEP amplitude 	Peak to peak amplitude of one MEP (Rossini and Rossi, 2007); a measure of the motor neurons in the corticospinal pathway that are activated by the TMS stimulus (Wassermann et al., 2008). MEP amplitude can assess the integrity and excitability of the corticospinal system (Rossini and Rossi, 2007).	Peak-to-peak amplitude, or maximum deflection-minimum deflection in a uV on EMG after a TMS pulse is given (Koski et al., 2007a).
MEP Latency 	The time from TMS stimulation until the onset of a MEP on the EMG recording (Wassermann et al., 2008). A measure of conduction time from TMS stimulation to MEP response (Rossini and Rossi, 2007).	Time from TMS stimulus to the first deflection in EMG (MEP onset – TMS onset) (Koski et al., 2007a).
Motor Threshold	The lowest TMS stimulation intensity needed to elicit a MEP (Wassermann et al., 2008); a measure of excitability of the membrane that surrounds the neuron (Chen, 2000), as well as "global excitability of the motor pathway" (Rossini et al., 2010).	Active threshold: minimum TMS intensity needed to elicit ≥ 200 μv MEP in half of the consecutive trials during active muscle contraction (Perez and Cohen, 2009). Resting threshold: minimum TMS intensity needed to elicit an MEP ≥ 50 μv in half the consecutive trials when at rest (Butler and Wolf, 2007).

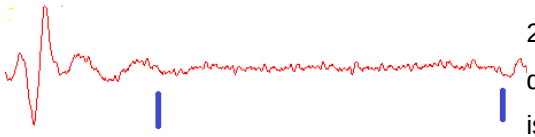
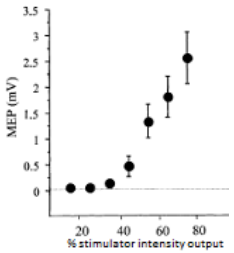
Silent Period 	The period after TMS stimulation of absent muscle activity on the EMG recording (Wassermann et al., 2008) The first part of the silent period may be in part due to spinal mechanisms, whereas the second part is thought to be due to cortical mechanisms; can be used to assess intracortical activity (Chen, 2000).	Visual assessment of EMG output using MEP onset to MEP return on EMG (Damron et al., 2008).
Recruitment Curve 	Incremental collection of MEP's with increasing stimulus intensity (Wassermann et al., 2008); a measure of neurons that are less excitable and farther from the centre of TMS activation (Chen, 2000).	Sequential collection of MEP's. The TMS intensity will begin at active motor threshold (100%) and will be increased by 10% of motor threshold until 130% of motor threshold is reached (Wassermann et al., 2008). Five trials obtained at each intensity.

Table 3 Describes the individual elements of the MEP that can be measured using single pulse TMS which are MEP amplitude, MEP latency, motor threshold, silent period, and recruitment curve. MEP=motor evoked potential, TMS=transcranial magnetic stimulation

1.8 **Neural plasticity**

Neural plasticity is the process of re-organisation of neural connectivity as a result of experience or practice (Warraich and Kleim, 2010); it is an everyday occurrence and the process by which we learn new tasks, and re-learn old tasks. Neural plasticity is most rapid in the early stages of development; the rate decreases as we age but is always present (Ward and Frackowiak, 2003). Neural plasticity can occur in both healthy adults and those with central nervous dysfunction arising from stroke. Neural plasticity occurs during novel skill learning in which the task must be complex and challenging in order for the brain to re-organise (Adkins et al., 2006). When we learn new tasks or improve our ability at a task new neural connections within the brain are created. One of the theories by which new neuronal connection are created is based on Hebian plasticity in which synaptic plasticity is strengthened through activation of the neuron (Takeuchi and Izumi, 2015). Hebian plasticity involves two processes, the first is long-term potentiation (LTP) and the second is long term depression (LTD). LTP is the strengthening of neuronal connections which can occur during exercise, repetitive task practice, or when learning a new task. Long term depression occurs when activity between neurons becomes slow or non-existent, these connections no longer become useful and thus become latent (Butler and Wolf, 2007).

Neural plasticity and excitability of the corticospinal pathway can be influenced by neurotransmitters in different ways. Examples of the neurotransmitters that influence neural plasticity are gamma-Aminobutyric acid $GABA_A$ which is thought to inhibit neural plasticity, and n-methyl-Dasparate receptor, NMDA, which is thought to increase neural plasticity though the passage of sodium and calcium ions into nerve cells which leads to neuronal depolarization (MacDermott et al., 1986, Ziemann et al., 2004). The excitability of the corticospinal pathway as measured by the slope of the recruitment curve was investigated after administration of lorazepam, which is a $GABA_A$ enhancer, lamotrigine which is a sodium and calcium channel inhibitor (similar to inhibiting NMDA), and d-amphetamine which has dopaminergic effects and is a medication used to enhance motor performance after stroke. Following drug administration the slope of the recruitment curve was enhanced by d-amphetamine, whereas, the slope was decreased by lorazepam and lamotrigine (Boroojerdi et al., 2001). Similarly, after administration of lorazepam ($GABA_A$ enhancer) and detromethrophan (an NMDA blocker) there were decreases in MEP amplitude with training (Bütefisch et al., 2000). Finally, intracortical inhibition was increased and MEP amplitude decreased after administration of lorazepam ($GABA_A$ enhancer) (Di Lazzaro et al., 2000). These findings suggest that excitability of the corticospinal pathway can be enhanced by dopaminergic medications, and inhibited by $GABA_A$.

The brains capacity for neural plasticity and cortical re-organisation may be in part related to physiology and genetics specifically a gene called brain derived neurotrophic factor, BDNF. Individuals with a morphism to the BDNF gene exhibited lower corticospinal excitability (measured by smaller MEP amplitudes) and decreased motor map re-organization after a training activity compared to individuals without the gene morphism (Kleim et al., 2006).

Finally, neural plasticity is specific to task training and motor learning. Research in animal models have demonstrated that general exercise without motor learning or task-specific trainings is not associated with an increase in synapses or changes in muscle motor map representation. However, general exercise demonstrated an increase in cortical angiogenesis (blood vessel density) (Kleim et al., 2002). Investigations in humans have demonstrated after task specific training there are associated increases in amplitude of MEP max and a decrease in motor threshold, indicating improved corticospinal excitability. In comparison there was no change in MEP max after two weeks of strength training, and at four weeks the amplitude of MEP max and slope of the stimulus-response curve decreased (Jensen et al., 2005). Similarly, in the lower limb motor skill training was associated with increased slope of the recruitment curve whereas, there was no change observed in the individuals that participated in passive training (Perez and Cohen, 2009). These findings support the theory that type and specificity of training influences the type of re-organisation within the brain and corticospinal pathway.

Neural plasticity is essential to learning in both neurologically intact adults and in stroke survivors. There are many processes that contribute to neural plasticity and cortical re-organisation such and LTP, LTD, neurotransmitters, physiology/genetics, and is specific to task practice. Understanding and exploring neural plasticity has become possible with the development of neuroimaging technologies and non-invasive brain stimulation, specifically through TMS.

1.9 Transcranial Magnetic Stimulation and neurologically intact populations

Transcranial magnetic stimulation studies in the neurologically intact population have helped researchers understand the role of the corticospinal pathway in active movement, assess neural plasticity and cortical re-organisation, and provide normative data for comparison to those with neurological disease.

Firstly, the findings of TMS studies in the neurologically intact population have helped develop an understanding of the connection between the motor cortex and the upper limb and cortical control of movement (Devanne et al., 2002, Levin et al., 2011, van Kuijk

et al., 2009a, Fujiyama et al., 2012, Pearce et al., 2000). The assessment of motor performance in racket ball players found that elite players had larger hand motor maps, lower motor thresholds, and increased MEP amplitudes compared to less skilled players (Pearce et al., 2000). This suggests improved skill level is associated with stronger corticospinal connections to the motor cortex. TMS can also be used to better understand interhemispheric connections between the right and left sides of the brain through interhemipsheric inhibition or facilitation (Kossev et al., 2002, Marneweck et al., 2011, Perez et al., 2004). Interhemispheric balance after stroke; exploring interhemispheric connections in neurologically intact individuals provides a range of "normal" function, and a way to induce inhibition or facilitation to probe what may be occurring after stoke.

Secondly, TMS has been used to evaluate neural plasticity in the neurologically intact brain. For instance, after completing wrist exercises, individuals exhibited increased corticomotor excitability for up to 30 minutes (Narayana et al., 2014) Individuals who learned a piano skill exercise demonstrated decreased motor thresholds, and increased cortical maps indicating increased corticospinal pathway excitability and neural plasticity. The decreased motor thresholds and increased cortical maps were associated with improved skill performance at piano playing through decreased errors (Pascual-Leone et al., 1995). There have been similar findings in investigations in the lower limb. A group of individuals completed thirty-two minutes of skilled ankle training involving dorsiflexion to move a cursor on a computer screen. After completing the skill training individuals demonstrated increased MEP amplitudes and decreased short-latency intracortical inhibition compared to baseline (Perez et al., 2004).

Thirdly, rTMS can be delivered to facilitate or inhibit specific brain areas; researchers can probe through a motor task or memory task to assess if performance has improved or declined. Thus researchers can induce "virtual lesions" in a specific brain region to better understand the role of that brain area. For example, inhibitory rTMS delivered to the primary motor cortex was associated with decreased motor function in the ipsilateral hand of healthy subjects (Vollmer et al., 2015), whereas facilitatory rTMS was associated with improved motor skill learning (Narayana et al., 2014).

TMS studies within the neurologically intact population have provided knowledge of the excitability of the corticospinal pathway, the role of different brain areas in motor function, and cortical re-organisation related to task specific training. The knowledge gained through TMS studies can be used as normative data for comparison to individuals with neurological disease such as stroke. However, these studies have focused on young neurologically intact adults, whereas the majority of stroke survivors are older adults, and the incidence of stroke increases with age (Xanthakis et al., 2014). There is evidence

that the natural ageing process is associated with changes within the CNS and decreases in motor function. Therefore, it is important to explore TMS in neurologically intact older adults as the response may be different to younger adults, and would provide age-matched comparison to those with neurological disease.

1.10 **Ageing**

The natural ageing process is associated with changes in the nervous system such as a decrease in white matter, interhemispheric connections via the corpus collusum, tissue density, myelination, and number of myelinated neurons within the corticospinal pathway (Seidler et al., 2010, Salat et al., 2005). There are also decreases in motor function with age that are associated with changes in brain activation. The changes in motor function with age are decreased dexterity of both the upper (Dayanidhi and Valero-Cuevas, 2014, Lawrence et al., 2014) and lower limbs (Lawrence et al., 2014); decreased reaction time (Levin et al., 2011, Poston et al., 2009), and muscle weakness (Plow et al., 2014). Research using fMRI has found that older adults recruit additional brain areas (Mattay et al., 2002, Talelli et al., 2008a) and additional neurons (Kossev et al., 2002) to complete the same task as younger adults. It is hypothesized that the additional areas and neurons are recruited to maintain a specific level of motor control or coordination for the task. In reaction time tasks, older adults demonstrated earlier activation of the corticospinal pathway compared to the younger adults and also had slower reaction times (Levin et al., 2011). Similarly to the over activation hypothesis, the earlier activation of the corticospinal pathway may be an attempt to improve or speed up reaction time. Older adults that demonstrated poorer dexterity also had decreased tissue density and decreased myelination of the axons in the internal capsule through which the corticospinal pathway passes (Sullivan et al., 2010). Muscle weakness with age has also been associated with TMS measurement. In older adults the centre of gravity of the biceps muscles was shifted anteriorly in the motor cortex and the centre of gravity was predictive of biceps strength (Plow et al., 2014). It is hypothesised that the anterior shift in the centre of gravity is due to compensatory mechanisms in an attempt to maintain strength. These findings highlight that there may be a link between age-related changes in the corticospinal pathway and arm and hand function that can be measured using TMS.

Transcranial magnetic stimulation in stroke survivors has been used to investigate the integrity and excitability of the corticospinal pathway after stroke, evaluate neural plasticity following a rehabilitation intervention, and in prediction of upper limb motor recovery such that the presence of an MEP early after stroke associated with better functional outcomes.

1.11 **Motor Evoked Potential and stroke**

There are changes with the MEP elements after a stroke, and the MEP elements are sensitive to measure change in corticospinal pathway excitability. Each MEP element will be discussed individually.

Following a stroke, the MEP amplitude is decreased compared to neurologically intact adults, reflecting a smaller number of neurons are activated by the TMS stimulus (Cacchio et al., 2011, Tarkka et al., 2008). The amplitude is sensitive to change following upper limb rehabilitation in stroke survivors, such as an increase in amplitude reflects a greater number of activated neurons and thus neural plasticity (re-organisation) (Butler and Wolf, 2007). For example, after six sessions of goal-oriented therapy MEP amplitude was increased 50% from the baseline assessment (Koski et al., 2004). Likewise, following two weeks of constraint inducted movement therapy MEP amplitude was increased from baseline (Park et al., 2004, Tarkka et al., 2008).

After a stroke, the MEP latency is longer compared to neurologically intact individuals (Butler and Wolf, 2007, Cacchio et al., 2011, Wheaton et al., 2009). The longer latency is thought to be due to damage of the fast conducting tracts of the corticospinal pathway as a result of the stroke (Turton et al., 1996); thus the neural impulses may use alternative pathways which may be inefficient, lengthening the time for the impulse to reach the muscle (Rossini et al., 2010). There is conflicting evidence concerning whether the MEP latency changes in response to an upper limb rehabilitation intervention. A longitudinal study monitored stroke survivors' upper limb function and corticospinal pathway excitability, demonstrating that as participants' strength improved their MEP latency decreased (Turton et al., 1996). Conversely, participation in two weeks of constraint induced movement therapy led to no difference in MEP latency from baseline to post-therapy (Tarkka et al., 2008).

The silent period can be lengthened after a stroke and changes over time. Brouwer and Schryburt-Brown (2006) found the silent period to be lengthened on the paretic side; and with time (recovery) the silent period duration shortened (Brouwer and Schryburt-Brown, 2006). Prolonged silent period is thought to be due to an imbalance of intracortical inhibitory networks within the brain such that there is increased neural activity in the unlesioned hemisphere and decreased neural activity in the lesioned hemisphere (Bütefisch, 2004).

Stroke survivors have higher motor thresholds requiring a stronger TMS stimulus to elicit a MEP compared to neurologically intact adults (Brouwer and Schryburt-Brown, 2006, Turton et al., 1996). The higher stimulus may be needed because of damage to the integrity of the corticospinal pathway, use of alternative pathways, or imbalance in intracortical connections. There is conflicting evidence on motor threshold response to

physiotherapy intervention. Sawaki and colleagues (2008) found no change in motor threshold after constraint induced movement therapy (Sawaki et al., 2008). Whereas Koski and colleagues (2004) found an immediate decrease in motor threshold following constraint induced movement therapy (Koski et al., 2004).

After a stroke, the slope of the recruitment curve has been found to be decreased in hand muscles compared to neurologically intact adults (Koski et al., 2007a). There is evidence that after two weeks of constraint induced movement therapy there was no change in the recruitment curve post therapy compared to baseline (Sawaki et al., 2008).

In addition to TMS being used to assess the integrity of the corticospinal pathway, and its response to physical therapy intervention TMS is being used as a measure to predict upper limb motor recovery after stroke.

1.12 Transcranial Magnetic Stimulation and prediction of recovery

Stroke survivors and their family members frequently ask therapists and physicians: “Will I return to my prior level of function I had before the stroke?” The answer to this question is also meaningful to clinicians to aid in patient and family education and in clinical decision making. Prediction of motor outcomes is becoming more important for discharge planning, and determining the optimal physiotherapy intervention. Previous research has utilised the initial level of paresis as a predictor of recovery. For example the less initial paresis (better movement) of the upper limb was a strong predictor of regaining dexterity (Hendricks et al., 2002, Kwakkel et al., 2003). In addition to initial paresis there is evidence that the presence of a MEP early after stroke is associated with improved motor recovery (Delvaux et al., 2003, Stinear et al., 2012); this is supported by the findings of a systematic review that demonstrated the presence of a MEP in the first few days after stroke was highly predictive of motor recovery (Hendricks et al., 2002). Previous research utilising an MEP to predict recovery has focused on an MEP in a muscle of the hand, the presence of an MEP in more proximal muscles has also been investigated. The findings demonstrate the presence of a MEP in the abductor digiti minimi was a better predictor of return of hand function versus the presence of a biceps MEP (van Kuijk et al., 2009b). This is not surprising as the specificity of the muscles are different. Finally, combining the presence of arm movement with presence of a MEP was an effective predictor of function (Stinear et al., 2012, van Kuijk et al., 2009b).

Neural plasticity after stroke is different to that of neurologically intact individuals. After a stroke there are physiologic changes within the brain and central nervous system to assist in repair and preservation of brain function.

1.13 **Neural plasticity after stroke**

Neural plasticity is an everyday occurrence by which the neurologically intact population learns new tasks, and improve skills in existing tasks. Neural plasticity for stroke survivors is essential to re-gain motor function and functional use of their body through new neuronal connections. The different phases of stroke recovery exhibit different rates of neural plasticity. Research in neural plasticity in the early phases of stroke recovery has been focused on animal models due to complexities of the research in humans. The use of neuroimaging and non-invasive brain-stimulation has provided knowledge of the underlying processes of neural plasticity in humans.

1.13.1 **Spontaneous recovery in animal models**

Spontaneous recovery is natural recovery (neural plasticity) that occurs early after stroke for around three months (Cramer, 2008); that can be enhanced through active participation in rehabilitation early after stroke (Buma et al., 2013). The mechanisms of spontaneous recovery are difficult to research in humans. However, animal research has provided insights into structural and molecular changes that may contribute to spontaneous recovery. In rats induced with a cortical stroke, in the initial 7 days after stroke there was a reduction in immunoreactivity including decrease of y- aminobutyric acid ($GABA_A$) receptors in the area surrounding the lesion and in connected brain regions with an increase in N-methyl-D-asperate (NMDA) (Redecker et al., 2002, Que et al., 1999). The importance of $GABA_A$ is that it is an inhibitory neurotransmitter which serves to block nerve impulses. Therefore, a decrease in $GABA_A$ in the first days after stroke would allow increased neuronal impulses and possibly facilitate neural re-organization. Along with a reduction in $GABA_A$ there is an increase in growth factor in the infarct area. Following an induced stroke in the rat, there was an increase in fibroblast growth factors in the brain tissue surrounding the lesion that continued for at least two months (Finklestein et al., 1990). Growth factors may contribute to the cellular processes involved in wound healing and in healing the damaged tissue surrounding stroke. An inflammatory response is the body's first defence mechanism; acutely after stroke there is inflammation within the peri-lesional brain tissue and there can be widespread inflammation throughout the brain. Inflammation can contribute to neuronal loss acutely, but in the long term it may contribute to repair and recovery (Lucas et al., 2006). Diaschisis occurs acutely after stroke, resolving over time. Diaschisis refers to any changes within the brain initiated by the stroke lesion itself but occurring in distant brain regions (Witte et al., 2000), such as a stroke in the primary motor cortex can be associated diaschisis in the cerebellum leading to decreased coordination of movement. The processes of immunoreactivity, influx of neurotransmitters (GABA and NMDA), inflammation and diaschisis may create an environment in the brain suitable for accelerated re-organization and neural plasticity early after stroke (Nudo, 2006).

1.14 **Cortical-reorganization after stroke**

Different phases of recovery after stroke have been identified. Initially after stroke there is the acute reaction to ischemia involving changes in blood flow, oedema, and inflammation in the area surrounding the lesion, which is similar to findings of animal studies (Wahl and Schwab, 2014). In addition to the acute reaction, Wallerian degeneration can occur within the corticospinal pathway and remote connections with the motor cortex. Wallerian degeneration is the disintegration of axonal structures, influx of macrophages, breakdown of myelin, and fibrosis leading to the atrophy of the fibre tract. Wallerian degeneration can start within three days after stroke and progresses with time (Thomalla et al., 2005, Xie et al., 2012). The degree of Wallerian degeneration is associated with motor impairment (Thomalla et al., 2004).

The second phase starts within the first days after stroke and lasts for weeks; this phase includes spontaneous recovery. This phase is characterised by hyperactivity in cortical areas such as motor, language, and attention areas; which decreases over time, and is associated with better motor outcomes (Wahl and Schwab, 2014, Cramer, 2008). For example, using fMRI and PET scanning acutely after stroke, there are greater number of active brain areas during a dexterity task compared to healthy controls; the increased activation decreased over 3-6 months (Marshall et al., 2000, Calautti et al., 2001). Additionally, stroke survivors demonstrate over-activation of the contralesional hemisphere altering the interhemisphic balance (laterality index) to the contralesional hemisphere (Tombari et al., 2004), Marshall et al. (2000). A recent meta-analysis demonstrated that stroke survivors consistently exhibited over-activation of their contralesional primary motor cortex, bilateral ventral premotor cortex and supplementary motor area compared to healthy adults (Rehme et al., 2012). Over time, cortical activation shifts back to the ipsilesional hemisphere and the interhemispheric balance (laterality index) is normalised (Marshall et al., 2000, Tombari et al., 2004). During the early phase of recovery, TMS studies have demonstrated that stroke survivors have increased motor thresholds (Cacchio et al., 2011, Wheaton et al., 2009) , decreased excitability of the corticospinal pathway exhibited by smaller MEP amplitudes (Cacchio et al., 2011, Wheaton et al., 2009), decreased slope of the recruitment curve (Koski et al., 2007a), and decreased intracortical inhibitiory mechanisms (Duque et al., 2005). Unmasking of latent pre-existing neuronal connections could contribute to cortical-reorganization early after stroke (Butler and Wolf, 2007). In rat models decreased cortical inhibition led to an increased in neuronal activity adjacent to the lesion (Jacobs and Donoghue, 1991). In human studies following CIMT the centre of gravity of the motor map area of the hand shifted posteriorly and laterally from baseline (Park et al., 2004); demonstrating adjacent neurons taking over the role (function) of the stroke impaired neurons. The processes of hyperactivity of cortical areas, decreased

corticospinal pathway output, and changes in inter-hemispheric balance are thought to be related to spontaneous recovery (Cramer, 2008, Wahl and Schwab, 2014).

The third phase begins weeks to months after stroke and is characterised by plateauing of spontaneous recovery. However neural plasticity continues into the chronic phases albeit more slowly (Wahl and Schwab, 2014, Cramer, 2008). Neural plasticity or re-organisation can occur through parallel pathways or new brain regions taking over the function of the damaged area (Chen et al., 2002, Wahl and Schwab, 2014). Research in rats has demonstrated that adjacent to the lesion there is axonal sprouting which is associated with improved limb use (Carmichael et al., 2001). An example in humans of cortical re-organisation through activation of existing but silent synapses (Butler and Wolf, 2007) is after task oriented training. Following task oriented training stroke survivors demonstrated increased activation contralaterally to the paretic limb (SMC) with associated decreased ipsilesional activation (Jang et al., 2003). Control of the movement after training shifted back to the lesioned hemisphere though activation of new neurons possibly through the process of LTP driven by task oriented training.

Recent research suggests that after a stroke, brain re-organisation within the lesioned hemisphere is associated with faster and better functional outcomes compared to re-organisation within the contralesional hemisphere (Calautti et al., 2001, Feydy et al., 2002, Loubinoux et al., 2003, Pundik et al., 2015, Turton et al., 1996, Ward et al., 2003). Additionally, individuals with damage to the corticospinal pathway were found to have greater motor deficits (Wenzelburger et al., 2005, Ward et al., 2007, Stinear et al., 2012). Patterns of activation identified with serial fMRI have provided knowledge of neural plasticity and functional recovery. Thus individuals with poorer motor function demonstrate neural activation of the unlesioned hemisphere during movement. Activation of the unlesioned hemisphere can also be investigated though TMS targeting ipsilateral corticospinal pathways.

1.14.1 **Ipsilateral pathway**

Most fibres of the corticospinal pathway cross contra-laterally about the level of the medulla, resulting in the right side of the brain activating (controlling) mostly the muscles of the left side of the body. In the general population the corticospinal pathway can contain up to about 30% of fibres that do not cross contra-laterally across the body leading to ipsilateral innervations of the upper limb muscles (Nathan et al 1990). In neurologically intact adults the ipsilateral projections are more prominent in the proximal upper limb muscles (Bawa et al 2004, Jankowska & Edgley 2006). Following neurological injury or pathology, ipsilateral connections to both proximal and distal muscles can be enhanced compared to neurologically intact adults (Bawa et al., 2004,

Jankowska and Edgley, 2006). Stroke survivors with ipsilateral connections demonstrate poorer motor function (Feydy et al., 2002, Turton et al., 1996).

The ability for our brains to form new connections is essential for motor recovery after stroke. The corticospinal pathway provides the connection between the motor cortex and the muscles of the arm and hand and is essential for functional use of the upper limb such as for reach-to-grasp. The integrity (excitability) of the corticospinal pathway can influence motor function, and measurement of the integrity of corticospinal pathway can give insight in to the pyramidal motor system (Bütefisch, 2004). Understanding the corticospinal pathway's contribution to movement, how it is changed after a stroke, and neural plasticity after rehabilitation can help direct specific interventions to improve neural control and improve successful reach-to-grasp. All muscles of the upper limb are necessary for successful reach-to-grasp, however TMS research has focused on the distal muscles, therefore less is known about the corticospinal connections to proximal muscles.

1.14.2 **Assessment of upper limb muscles**

Previous TMS research in both healthy and stroke populations have focused on investigation of distal upper limb muscles such as the hand and forearm muscles (Malcolm et al., 2006, Koski et al., 2007a, Koski et al., 2005, Liu and Au-Yeung, 2014, Hoonhorst et al., 2014). There has been less research on the proximal upper limb muscles for example the biceps. The proximal upper limb muscles are essential to transport the hand to allow for grasp and object manipulation, and to maintain stability while the distal joints are mobile (Lum et al 2008, Alt Murphy 2015, Shumway-Cook and Wollacot 2007). The biceps muscle is commonly impaired after a stroke and therefore the target of many upper limb interventions (Pundik et al., 2015, Donaldson et al., 2009, Wolf et al., 2006) thus warranting investigation. There is evidence that the different muscles of the upper limb receive different corticospinal input and respond differently to TMS (Martin et al., 2006, Malcolm et al., 2006). Therefore, both distal and proximal muscles should be investigated.

Transcranial magnetic stimulation can provide knowledge of the integrity or excitability of the corticospinal pathway, cortical-reorganisation following a rehabilitation intervention, predictor of upper limb motor function, and determine if there are ipsilateral connections from the unlesioned hemisphere to the muscles of the more-affected upper limb. It is important when using a measurement tool such as TMS that it is reliable within the population. A reliable measurement tool ensures confidence in the results of the measurement and that the findings will be interpretable; this allows clinicians and researchers to make informed clinical decisions (Bruton et al., 2000, Portney and Watkins, 2009).

1.15 Reliability of TMS assessment of the corticospinal pathway to upper limb muscles

Reliability is a measure of consistency, repeatability, or agreement of a measure or measurement tool over at least two separate tests (Bruton et al., 2000, Portney and Watkins, 2009) and is based on the "proportion of the total observed variance that is attributable to error" (Portney and Watkins, 2009). There are several properties of reliability that can be assessed such as reliability, measurement error, and internal consistency (Mokkink et al., 2010). The studies within this thesis focus on reliability. Within reliability there is inter-rater reliability and intra-rater or test-retest reliability. Inter-rater reliability encompasses different raters, the same instrument, and the same sample (Kottner et al., 2011, Mokkink et al., 2010, Portney and Watkins, 2009). The inter-rater reliability of TMS measurement has been documented exhibiting ICC values ranging from 0.6 to 0.94 (Cacchio et al., 2009, Bastani and Jaberzadeh, 2012, Mylius et al., 2013). Intra-rater and test-retest reliability encompass the same rater, same instrument, and the same sample (Kottner et al., 2011, Mokkink et al., 2010, Portney and Watkins, 2009). Test-retest reliability is the agreement of a measurement taken on two separate occasions when no change in the population was expected (de Vet et al., 2006). The test-retest reliability of TMS measurement is of interest in the studies presented in this thesis.

A reliable measurement tool ensures confidence in the results of the measurement and that the findings will be interpretable; this allows clinicians and researchers to make informed clinical decisions based on a specific measurement (Bruton et al 2000, Luiz et al 2005, Portney and Watkins 2000). With any measurement there will be day-to-day variability and inconsistency; through statistical assessment it can be investigated if the variability is within acceptable limits. There are different statistical methods that can be used to investigate reliability and agreement between tests; previous research has used Pearson's correlation, Cohen's Kappa, Lin's Concordance Coefficient (CCC), Intraclass Correlation Coefficient (ICC), and the Limits of Agreement (LOA). Pearson's correlation evaluates the strength of the association between two measurements but is limited in that is does not evaluate agreement (de Vet et al., 2006), Cohen's Kappa is useful in the reliability of categorical or ordinal data whereas TMS data is ratio data, and CCC is used to investigate two different methods, raters, or instruments (Portney and Watkins 2009). The ICC measures the degree of correlation and agreement between ratings making it a better statistical assessment of reliability than Pearson's correlation (Bruton et al., 2000, de Vet et al., 2006, Portney and Watkins, 2009). The LOA and Bland-Altman plots assess agreement across tests and evaluate if there is a biased pattern of error (underestimating or overestimating the true score) (Portney and Watkins, 2009, Bland and Altman, 1986b). Interpreting the ICC and LOA together can provide information

about both the reliability and potential differences in TMS values between tests. Acceptable reliability in the studies in this thesis are interpreted such that the ICC value of > 0.70 for the lower end of the confidence interval is acceptable reliability (Portney and Watkins, 2009, Schambra et al., 2015).

The test-retest reliability of TMS measures has been investigated in neurologically intact young adults, and in stroke survivors greater than six months post stroke. There is a knowledge gap of the test-retest reliability in older adults and stroke survivors early after stroke.

1.15.1 **Reliability of TMS measures in neurologically intact adults**

In neurologically intact adults, the test-retest reliability of TMS measures is variable, ranging from poor to good depending on the MEP element and target muscle being investigated. The findings of individual studies are in Table 4. The motor threshold demonstrates the highest ICC values for example, for the first dorsal interosseous (FDI) the ICC ranges from an ICC=0.81 (95% Confidence Interval (CI) 0.50-0.93) (Liu and Au-Yeung, 2014) to an ICC=0.98 (CI not reported) (Koski et al., 2005). The MEP amplitude demonstrates lower ICC values, such as for the FDI ranging from ICC=0.53 at 110% AMT to (Ngomo et al., 2012), to ICC=0.87 (0.60-0.96) (Liu and Au-Yeung, 2014).

There is evidence of age related changes with the brain and corticospinal pathway (Seidler et al., 2010, Salat et al., 2005) and associated changes in motor function (Dayanidhi and Valero-Cuevas, 2014, Lawrence et al., 2014, Plow et al., 2014). In addition to age related changes in the CNS, there are changes within MEP element measurement with age, however, the evidence is inconsistent Figure 4. It is unknown how age-related changes in the central nervous system may influence the reliability of TMS measurement. It is possible that with age, excitability of the corticospinal pathway is more variable. Therefore, the test-retest reliability in younger adults may not be applicable to older adults. The test-retest reliability of TMS measure in neurologically intact adults of all ages needs to be explored. Knowledge generated would provide understanding of how age may influence reliability of TMS measures, provide age-matched data for comparison to individuals with neurological disease, and improve our understanding of the corticospinal pathway.

Figure 4 - The influence of age on MEP elements

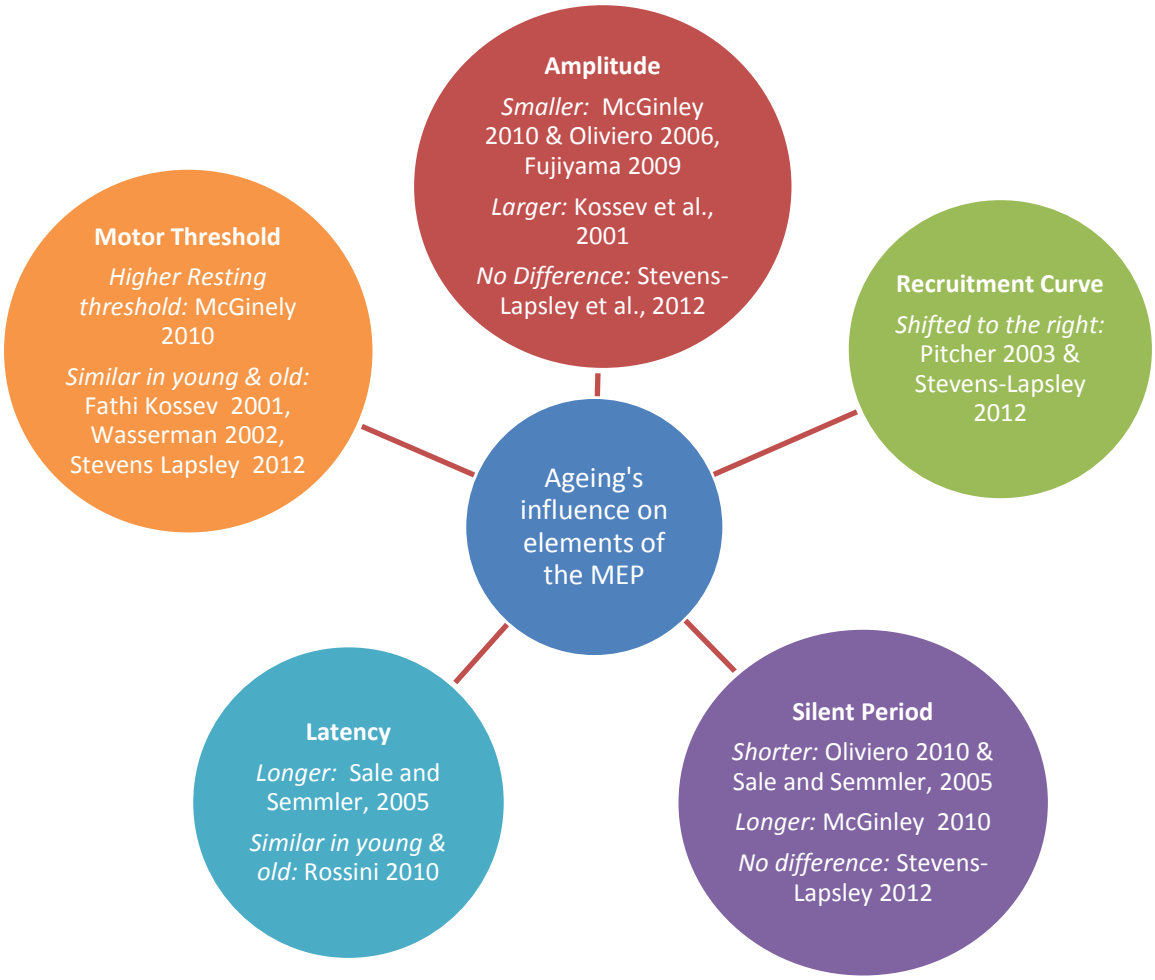


Figure 4 Describes the changes with the elements of the motor evoked potential within the healthy aging nervous system

Table 4 - Reliability of TMS measures in neurologically intact adults

Study	Type of reliability	Sessions and Raters	TMS stimulator and coil	Participants	Muscle	MEP amplitude	MEP latency	Silent Period	Recruitment Curve	Motor Threshold
Liu 2014	Test-retest	1 rater: 2 sessions with a week interval between sessions	MagStim with a 70mm figure-of-8 coil	N=14 27.4±3.4 years of age	FDI	(ND Peak) ICC=0.87 (0.60-0.96)			(ND) ICC=0.75 (0.23-0.92)	(ND)ICC=0.81 (0.50-0.93)
Carroll 2001	Test-retest	2 sessions separated by at least 24 hours	MagStim 200 figure-of-eight coil with 8 cm loop	N=8 22-36 years of age	FDI	(D Peak) ICC [A,3] ICC=0.82 ICC [A,1] ICC=0.60			(D) slope ICC [A,3] ICC=0.91; ICC [A,1] ICC=0.77 Peak slope: ICC [A,3] ICC=0.84 ICC [A,.1] ICC=0.63 X intercept ICC [A,3] ICC=0.93 ICC [A,1] ICC=0.81	ICC [A,3] (D) ICC= 0.96 ICC [A,1] ICC=0.89
Koski 2005	Test-retest	3 raters; 7 sessions over 10 hours (1.5 hours between sessions)	Magstim Super rapid biphasic stimulator; figure-of-eight coil; 9 cm per wing	N=17 (19-36 years of age)	FDI			(CSP) (D) ICC=0.99 (ND) ICC= 0.83		(D) ICC=0.98 (ND) ICC=0.97

Study	Type of reliability	Sessions and Raters	TMS stimulator and coil	Participants	Muscle	MEP amplitude	MEP latency	Silent Period	Recruitment Curve	Motor Threshold
Ngomo 2012	Test-retest Short term (ST) and long term (LT)	3 sessions, 4 days between session 1 and 2, and 35 to 457 days between sessions 2 and 3	Neuronagivated TMS MagStim BiStim 70mm figure-of-eight coil	N=12 26.5±4.3 years of age	FDI	**ST:** (D) R110% ICC=0.70 A 110% ICC=0.53 R 120% ICC=0.87 A120% ICC=0.66 **LT:** R110% ICC=0.20 A 110% ICC=0.79 R 120% ICC=0.75 A120% ICC=0.63				(ND) rMT ICC=0.89 (ND) aMT ICC=0.89
Solloman 2013	Inter-rater (IER) Intra-rater (IAR)	2 raters 3 sessions (session 1 and 2 same investigator)	Neuronavigated TMS eCimia 4.3 Nexstim biphasic figure-of-eight coil 50 mm radius	N=10 24.2(22.7-30.3 years of age)	APB					(IER D) CCC= 0.709 (0.244-0.909) (IAR D) CCC=0.725 (0.276-0.914)
Christie 2007	Test-retest	2 sessions separated by 20 minutes	Cadwell stimulator 7 cm circular coil (used same hot spot)	N=30 76±6.3 years of age	ADM	1.1x MT ICC=0.83 1.2x MT ICC=0.65 1.3x MT ICC=0.82				
Malcolm 2006	Test-retest	2 sessions separated by 2 weeks	MagStim 200 circular coil	N=20 26.9±4.5 years of age	FDI APB EDC FCR				(D slope) ICC=0.82 ICC=0.78 ICC=0.83 ICC=0.60	

Study	Type of reliability	Sessions and Raters	TMS stimulator and coil	Participants	Muscle	MEP amplitude	MEP latency	Silent Period	Recruitment Curve	Motor Threshold
Damron 2008	Inter-rater	2 sessions separated by 3 weeks	MagStim 200^2	N=9 Men 22.1±0.03 years Women 24.1±1.5 years	FCR			(ND) ICC=0.91-0.99, CV 11.4-32.5		
Cacchio 2011	Test-retest	One rater 2 sessions 4 week interval between sessions	Magstim 200 circular coil	N=16 63.1±10.1	TA	(D) ICC=0.88 (0.65-0.96) (ND) ICC=0.88 (0.66-0.95)	(D) ICC=0.95 (0.82-0.98) (ND) ICC=0.90 (0.73-0.97)			(D) ICC=0.95 (0.89-0.98) (ND) ICC=0.93 (0.87-0.97)
Cacchio 2009	Intra-investigator (IAR) inter (IER)-investigator test-retest) (TRT) reliability	Intra-investigator (IAR): 2 sessions 1.5 hours apart, test-retest 4 weeks between sessions	Magstim 200 circular coil	N=50 22-74 years of age	TA	(D) MEP max IAR ICC=0.75(0.71-0.79) IER ICC=0057 (0.64, 0.76) TRT ICC=0.73 (0.71-0.75)	(D) IAR ICC=0.93 (0.88, 0.97) IER ICC=0.79 (0.76,0.83) TRT ICC=0.92(0.84-0.98)	(D) Max: IAR ICC=0.95 IER ICC=0.89 (0.85, 0.94) TRT ICC=0.95 (0.88-0.99) Min: IAR ICC=0.79 (0.76,0.83) IER ICC=0.81 (0.78, 0.84) TRT ICC=0.81 (0.78-0.85)	(D slope) IAR ICC=0.79 (0.72-0.84) IER ICC=0.66 (0.62,0.78) TRT ICC=0.78 (0.72-0.83)	(D) IAR ICC0.98(0.93-0.99) IER ICC=0.94(0.89-0.98) TRT ICC=0.97 (0.90-0.99)

Study	Type of reliability	Sessions and Raters	TMS stimulator and coil	Participants	Muscle	MEP amplitude	MEP latency	Silent Period	Recruitment Curve	Motor Threshold
Schambra 2015	Test-retest	1 rater 4 sessions 1 AM, 1 PM then repeated the next day	Magstim BiStim^2 with phantom MRI 70mm figure-of-eight coil		FDI				Slope (left) 0.03 (0, 0.51) (right) ICC=0.07 (0,0.70) Plateau (left) ICC=0.90(0.82, 0.094) (right) ICC=0.82 (0.62, 0.94) S_{50} (left) ICC=0.91 (0.80, 0.95) (right) ICC=0.92 (0.82,0.96)	(left) ICC=0.97 (0.90,0.99) (right) ICC=0.98 (0.96, 0.99)
Carson 2013	Test-retest	3 session each separate by at least 24 hours	Magstim 2000 70mm figure-of-eight coil	FDI n=8; 22-36 years of age FCR 11; 20-56 years of age FCR n=57; 18-47 years of age	FDI ECR FCR	(Max) FDI: ICC=0.85 FCR ICC=0.35 FCR ICC=0.06			Slope FDI: ICC=0.85 FCR: ICC=0.76 FCR ICC=0.36	
Kimiskidis 2004	Test-retest	1 rater 2 sessions of varied length between from 19 minutes to 1867±94 days	Magstim 200 70 mm figure-of-eight coil	N=82 12-65 years of age	FDI					Spearman brown formula to determine reliability coefficient 0.928; measurement error 8

Study	Type of reliability	Sessions and Raters	TMS stimulator and coil	Participants	Muscle	MEP amplitude	MEP latency	Silent Period	Recruitment Curve	Motor Threshold
Kamen 2004	Test-retest	3 sessions separate by at least 24 hours	Caudwell MES-10 9-cm focal coil	N=14 24.4±8.2 years	Biceps, FDI	Rest Biceps: 100% ICC=0.98 85% ICC=0.99 70% ICC=0.95 Rest FDI: 100% ICC=0.60 85% ICC=0.75 70% ICC=0.81 Active (70% stim output) Biceps: 25% MVC ICC=0.79 50% MVC ICC=0.68 75% MVC ICC=0.69 100% MVC ICC=0.68				

Table 4 - Reliability of TMS measures in neurologically intact adults describes the findings of the test-retest reliability of TMS measures. The table includes the type of stimulator and coil used for data collection, the time interval between sessions, number of sessions, number and age of participants, target muscle of assessment, and the ICC value of the MEP elements assessed. If the number of raters is not specified than it is assumed there was one rater. Acceptable reliability is interpreted such that an ICC value of > 0.70 for the lower end of the confidence interval is acceptable. ICC=intraclass correlation coefficient, CCC= Lin's concordance correlation coefficient, FDI= first dorsal interosseous, APB abductor pollicis brevis, ECR=extensor carpi radialis, FCR=flexor carpi radialis, EDC= extensor digitorum confundis, TA=tibialis anterior, ADM= adductor digiti minimi, D=dominant limb, ND=non-dominant limb, MVC=maximal voluntary contraction

1.15.2 **Reliability of TMS measures in stroke survivors**

The test-retest reliability of TMS measures in stroke survivors has been focused in chronic stroke populations who are greater than six months after stroke. There has been one recent study investigating the reliability of TMS measures in sub-acute stroke, however, it was limited to assessing only the FDI muscle. The findings of test-retest reliability in chronic stroke survivors are also variable, ranging from poor-good for the different MEP elements (Table 5).

The motor threshold demonstrates higher ICC values as in the FDI the ICC=0.97(0.94-0.99) (Liu et al 2014), on the other hand the MEP amplitude demonstrates lower ICC in the tibialis anterior the ICC=0.38 (-0.74-0.78) (Cacchio et al., 2011). Previous investigations have been limited to investigating mostly hand muscles, however, all muscles of the upper limb are essential for reach-to-grasp and to complete ADL's. In the first few months after stroke there are many physiological differences within the central nervous system including the initial inflammatory response, cortical hyperactivity, spontaneous recovery and rehabilitation or experience-dependent neural plasticity (Wahl and Schwab, 2014, Cramer, 2008, Marshall et al., 2000, Calautti et al., 2001). Neural plasticity continues in chronic stroke but at a slower rate (Kwakkel et al., 2003). Therefore, the test-retest reliability findings in the chronic stroke population may not be applicable to stroke survivors within in the first three months after stroke. It is important to determine the test-retest reliability of TMS within each population it is being used, to have confidence in the results of the measure to be able to make clinical decisions. TMS is being increasingly used in stroke research as a measure of neural plasticity and to predict upper limb function, thus the test-retest reliability of TMS in stroke survivors within the first three months after stroke needs to be determined.

1.16 **Summary**

In summary, improved stroke rehabilitation specifically upper limb rehabilitation is needed. Over half of stroke survivors are living with upper limb disability preventing their participation in ADl's. A deeper and more complete understanding of upper limb movement, the underlying movement deficits, and the neural correlates of movement is a first step in progressing rehabilitation. The kinematic differences between stroke survivors and neurologically intact control participants is expected to provide the underlying movement deficits during reach-to-grasp. Developing more targeted interventions aimed at the movement deficits may improve the efficiency and decrease the cost of rehabilitation. Understanding the role of the corticospinal pathway to movement and motor control will provide the link between the CNS and the musculoskeletal system as well as movement control of the upper limb. TMS can be used to assess corticospinal pathway excitability, integrity, and contribution of

movement. Before TMS is widely used, its reliability needs to be determined. The test-retest reliability of previous TMS research has focused on young, neurologically intact adults and stroke survivors greater than six months after stroke. There is a gap of research in older adults and stroke survivors within the first few months after stroke. There is potential that the excitability of the corticospinal pathway may be variable in older adults due to age related changes in the CNS and in stroke survivors early after stroke due to hyperactivity of motor areas, spontaneous recovery, and task-dependent neural plasticity. Therefore, the reliability of TMS measures needs to be determined in these populations.

Table 5 - Test-retest reliability of TMS measures in stroke survivors

Study	Reliability and Raters	Sessions and interval between	TMS stimulator and coil	Participants and time since stroke	Muscle	MEP amplitude	MEP latency	Silent Period	Recruitment Curve	Motor Threshold
Cacchio 2011	Test-Retest	2 sessions, 4 week interval	MAGSTIM 200 circular coil	N=16 21.6±14.8 months	TA	(L) ICC=0.38 (-0.74-0.78) (UL) ICC=0.87 (0.76-0.92)	(L) ICC=0.85 (0.58-0.94) (UL) ICC=0.91 (0.76-0.96)			(L) ICC=0.90 (0.72-0.96) (UL) ICC=0.92 (0.78-0.97)
Harris-Love 2013	Test-retest	2 sessions separate days			Biceps and Triceps			CSP (L) Biceps ICC=0.57 to 0.79 Triceps ICC=0.68 to 0.84		
Hoonhorst	Intra-observer (IA) Inter-observer (IE)	2 sessions 7 day interval		N=18 3.5 (3-5) months	APB		TMCT (L) IE: 0.772 (0.562 to0.905) IA: ICC=0.638 (0.247 to 0.853) IA: ICC= 0.585 (0.123 to 0.834)			
Liu 2014	Test-retest	2 sessions, 1 week interval		N=27, 7.6±3.2 years	FDI	(Peak MEP) (L) ICC=0.96(0.91-0.98) (UL) ICC=0.95 (0.88-0.98)		(L) ICC=0.88 (0.72-0.94) (UL) ICC=0.93 (0.85-0.97)	(Slope) (L) Slope ICC= 0.95 (0.88-0.98) (UL) ICC= 0.95 (0.89-0.98)	(L) ICC= 0.97 (0.94-0.99) (UL) ICC= 0.95 (0.89-0.98)

Study	Reliability and Raters	Sessions and interval between	TMS stimulator and coil	Participants and time since stroke	Muscle	MEP amplitude	MEP latency	Silent Period	Recruitment Curve	Motor Threshold
Koski 2007	Test-retest	2 sessions, 2 week interval		N=9 (mean) 12.8; range 8-17 months	FDI	(MEP max) (L) ICC=0.98; LLCI=0.94 (UL) ICC=0.71 LLCI=0.21			(peak slope) (L) ICC=0.98 LLCI=0.93 (UL) ICC=0.19 LLCI=negative range (Slope) (L) ICC=0.87 LLCI=0.57 (UL) ICC=0.78 LLCI=0.35	(of MEP max) (L) ICC= 0.84 LLCI 0.49 (UL) ICC=0.31 LLCI=negative range
Wheaton 2009	Test-retest	2 sessions, 7-10 day interval	MAGSTIM 200 double-cone coil	N=23 (median) 57.6 months	VL, VM	(L) VL ICC= 0.205 VM ICC=0.537 (UL) VL ICC=0.874 VM ICC=0.831		(L) VL ICC=0.689 VM ICC=0.789 (UL) VL ICC=0.791 VM ICC=0.645		(L) ICC=0.798 (UL) ICC=0.975
Schambra 2015	Test-retest, 1 rater	4 sessions (AM. PM) 1 day interval	Magstim Bistim^2 + phantom brain, figure-of-eight coil	Subacute n=20, 17.4±9.8 days Chronic n=21 2617.9±3166.1 days	FDI				Slope Subacute (L) ICC=0.70 (0.35, 0.84) (UL) ICC=0.53 (0.26, 0.77) Chronic (L) ICC=0.18 (0, 0.86) (UL) ICC=0.23 (0, 0.71)	Subacute (L) ICC=0.96 (0.91, 0.99) (UL) ICC=0.99 (0.98, 0.99) Chronic (L) 0.96 (0.93,0.98) (UL) 0.98 (0.96,0.99)

Table 5 - Test-retest reliability of TMS measures in stroke survivors describes the findings of the test-retest reliability of TMS measures of corticospinal pathway. The table includes the type of stimulator and coil used for data collection, interval between sessions, number of sessions, number of participants, times since stroke, target muscle, and the reliability of the MEP elements assessed. Acceptable reliability is interpreted such that an ICC value of > 0.70 for the lower end of the confidence interval

is acceptable. ICC=intraclass correlation coefficient, FDI= first dorsal interosseous, VL= vastus lateralis, VM=vastest medius, APB=abductor pollicis brevis, TA=tibialis anterior, L=lesioned hemisphere, UL=un-lesioned hemisphere

2 Statement of Aims

2.1 Statement of aims

The studies reported in this thesis are the need for a better understanding of the neuro-biomechanical correlates of reach-to-grasp. This is required because, despite participation in rehabilitation, up to 65% of stroke survivors do not recover the ability to reach, grasp, or transport objects as measured by impaired dexterity of their more-affected hand. As reach-to-grasp is an essential part of all activities of daily living such as dressing, grooming, and eating its absence clearly limits independent living. Consequently current rehabilitation interventions need to be improved upon.

Taking the first steps towards more effective upper limb rehabilitation is promised by targeting the underlying movement deficits with the intervention most likely to re-establish normative motor function. Enhanced understanding of the movement deficits in reach-to-grasp is expected to provide clearer definition of the targets for rehabilitation and thus enhance the specificity of rehabilitation for better functional ability outcomes. Kinematic assessment can identify the underlying motor components of normal movement and identify changes in these which are associated with movement deficit. For example, velocity, smoothness, and trajectory of reach-to-grasp.

Studies investigating the kinematics of reach-to-grasp utilise varied methodologies. For instance, varied reach-to-grasp task, movement speed, trunk restraint, and methods of data collection and analysis, demonstrate heterogeneity. Variation between studies makes it difficult for therapists to select which intervention may be the most effective for the individual. Further complexity arises because it is unknown how task requirements such as object location may impact kinematic characteristics. As a result erroneous diagnoses are possible.

There are reviews of reach-to-grasp kinematics and neural control of reaching but these are narrative. Systematic synthesis of reach-to-grasp kinematics after stroke compared to age-matched healthy adults with meta-analysis and consideration of risk of potential bias is lacking. This is needed to inform the development of a standardised reach-to-grasp assessment for better diagnosis and targeted interventions.

Already known is that successful reach-to-grasp is accomplished through the interaction of the nervous and musculoskeletal systems. Central to the interaction between the nervous and musculoskeletal systems is the corticospinal pathway, connecting the motor cortex to the muscles of the arm and hand. The corticospinal pathway is essential for smooth coordinated arm movement. Assessment of the corticospinal pathway is undertaken using transcranial magnetic stimulation; which is a painless brain stimulation technique based on the principles of electromagnetism. The response to a brief

magnetic stimulus over the primary motor cortex is a “natural” muscle contraction called a motor evoked potential (MEP) in the target muscle of investigation. The MEP is measured using electromyography, electrodes placed on the skin over the target muscle. Transcranial magnetic stimulation has been used with neurologically intact and stroke survivor adults. Such investigations demonstrate that after a stroke the integrity of the corticospinal pathway can be disrupted. Investigation of the motor evoked potential can provide researchers with information about the strength or excitability of the corticospinal pathway, and how excitability changes in response to learning or practicing a motor task (neural plasticity). Moreover, in stroke survivors the presence of a MEP early after stroke is being used as a research tool and is a proposed prognostic indicator of arm and hand recovery. However, the reliability (repeatability) of TMS measures early after stroke remains uncertain.

The reliability or repeatability of TMS measures has been investigated in young healthy adults. The test-retest reliability between sessions demonstrates moderate to good reliability in both populations. However, with age there are changes within the central nervous system such as decreased brain volume, decreased inter-hemispheric connections, and microstructure changes within the corticospinal pathway. It is unclear how these changes may influence aspects of the MEP and the reliability of TMS measurement in middle-aged and older adults. There is a paucity of TMS investigation of the corticospinal pathway connection with the proximal upper limb muscles such as the biceps that are essential for successful reach-to-grasp. Proximal upper limb muscles are essential to transport the hand in space, then to stabilize the arm while the hand and wrist are involved in object manipulation. Determination of the test-retest reliability of TMS measures in neurologically intact adults of all ages in both proximal and distal upper limb muscles is indicated. The findings of this investigation will contribute to a better understanding of: the functionality of the corticospinal pathway over the age span, test-retest reliability of TMS measures, and provide normative data to compare to stroke survivors, the majority of which are older adults.

The test-retest reliability of TMS measures has been investigated in stroke survivors who are at least six months after stroke. Extrapolation of these findings to people earlier after stroke is not possible because of the physiological differences in the brain such as: the initial inflammatory response, over activation of brain areas, and spontaneous recovery. It is uncertain how these processes impact the corticospinal pathway, and consequently TMS measures. There is a distinct lack of investigation of the reliability of TMS measures in people who are less than three months after stroke. Furthermore, just like the TMS investigations of corticospinal function in neurologically intact populations research with stroke survivors has investigated the distal muscles of the upper limb. As the proximal muscles are often impaired following a stroke they require research

examination, not least because TMS is being used in rehabilitation studies to assess neural plasticity and as a predictor of function early after stroke. Consequently, the reliability of TMS measurement in both proximal and distal upper limb muscles in people within three months after stroke needs to be determined.

Progressing the clinical science of comprehensive assessment and subsequent individualized treatment for stroke survivors is expected to enhance current levels of upper limb recovery. Synthesizing the knowledge of the kinematic deficits during reach to grasp, the corticospinal contribution to reach to grasp, the influence of targeted interventions on the corticospinal pathway, neural plasticity, movement kinematics, and upper limb function are therefore the areas of investigation of studies reported in this thesis.

2.2 Research questions

Question 1

Are kinematic characteristics during reach-to-grasp different between stroke survivors and neurologically intact controls and are the kinematic differences influenced by task requirements such as object placement?

This question was informed by the need to develop targeted upper limb interventions aimed at the underlying movement deficits of reach-to-grasp. Reach-to-grasp is part of all ADL's; improved interventions targeted at reach-to-grasp could contribute to improved independence with ADL's.

Aim 1a

Determine if kinematic characteristics such as movement time, peak velocity, trunk contribution, smoothness of movement, reach path ratio, and elbow range of motion are statistically different during reach-to-grasp comparing stroke survivors to neurologically intact adults.

Aim 1b

Determine the influence of task requirements such as object location, the time since stroke, and upper limb motor function on the kinematic differences between stroke survivors and neurologically intact adults.

Aim 1a and aim 1b will be investigated through a systematic review and meta-analysis (Chapter 3)

Questions 2a and 2b

Questions 2a and 2b are regarding the test-retest reliability of TMS measures in neurologically intact adults.

Question 2a

Is TMS measurement of corticospinal pathway excitability reliable (test-retest reliability) in neurologically intact adults of all ages (> 18 years of age)?

This research question was informed by the need to investigate the reliability of a measurement tool within all the populations that it is used. Many stroke survivors are older adults; the focus of TMS research and reliability research is in young adults. With age there are changes within the nervous system that may influence TMS measurement and its reliability; necessitating the need to investigate the reliability of TMS measurement in neurologically intact adults of all ages.

Aim 2a

Determine the reliability of the MEP elements of active and resting motor threshold, motor evoked potential amplitude, motor evoked potential latency, silent period, and a recruitment curve of the bilateral biceps brachii, extensor carpi radialis and abductor pollicis brevis muscles in neurologically intact adults who are at least 18 years of age.

Question 2b

Is the reliability of TMS measurement influenced by age, gender, or physical activity?

This research question was informed by evidence that the corticospinal pathway and brain stimulation can be influenced by aging (decreased brain volume, decreased intracortical connections, decreased myelination and density of neurons within the corticospinal tract), physical activity (greater corticospinal excitability), and gender (female hormones can influence neural plasticity).

Aim 2b

Explore if the test retest reliability of the motor threshold is different in older adults, men or women, and individuals that exercise. Furthermore, the reliability of additional TMS measures (MEP amplitude, MEP latency, and silent period) for each group (older adults, men, women, exercisers and non-exercisers) will be provided in the appendix of the thesis. The study is not powered to determine a statistical difference for each group of individuals. The main text will discuss the reliability of TMS measures in the group as a whole.

Aim 2a and aim 2b will be investigated through a prospective correlational test-retest reliability study of TMS measures in neurologically intact adults, lifestyle factors questionnaire and the Nine Hole Peg Test (Chapter 4).

Question 3

Is TMS measurement of corticospinal pathway excitability reliable (test-retest reliability) in a group of sub-acute stroke survivors?

This research question was prompted by research that the rate of neural plasticity is more rapid in the early months after stroke (first three months) compared to later after stroke (> six months after stroke). A measurement tool must be reliable within the population it is being used. The test-retest reliability findings later after stroke may not be applicable to stroke survivors within the first three months after stroke.

Aim 3

Determine the test-retest reliability of TMS measures of corticospinal pathway excitability such as: active and resting motor threshold, motor evoked potential amplitude, motor evoked potential latency, silent period, and a recruitment curve of both the more-affected and less-affected biceps brachii, extensor carpi radialis and abductor pollicis brevis muscles in stroke survivors two to sixty days after stroke

Aim 3 will be investigated through a prospective correlational test-retest reliability study of TMS measures of corticospinal pathway excitability in stroke survivors who are two to sixty days after stroke (Chapter 5).

3 Getting a kinematic handle on reach-to-grasp: A systematic review and meta-analysis

3.1 Introduction

A recent systematic review concluded that the optimal upper limb therapy to enhance upper limb function after stroke remains unknown (Pelton et al., 2012). This could be because the movement deficits resulting from stroke and subsequent recovery are heterogeneous (Kwakkel and Kollen, 2013). Consequently, interventions targeted at specific movement dysfunction could be beneficial for upper limb recovery.

Reach-to-grasp is an important focus for rehabilitation as it is a vital component of many activities of daily living (ADL's) such as grooming and dressing. Reach-to-grasp has been studied extensively in adults with and without neurological disease (Bennis and Roby-Brami, 2002, Messier et al., 2006, Gilster et al., 2012, van Vliet and Sheridan, 2007, van Vliet and Sheridan, 2009). Successful reach-to-grasp is achieved through coordination of the nervous and musculoskeletal systems. The nervous system provides the motor plan, muscle activation, and directs movement adjustments based on peripheral feedback (e.g. visual, proprioceptive, and kinaesthetic). The musculoskeletal system contributes the muscle activity and joint motion necessary for movement control (McCrea et al., 2002, Shumway-Cook and Woollacott, 2007). Reach-to-grasp can be quantitatively assessed using kinematic analysis which is a sensitive, objective, and reliable measure of upper limb movement (Caimmi et al., 2008, Lum et al., 2009, Nowak, 2008, McCrea et al., 2002, Patterson et al., 2011, Platz et al., 1999). Kinematic analysis can provide understanding of movement control by determining the underlying mechanisms of movement or movement deficit. In addition kinematic analysis provides sensitive measures of movement control (Caimmi et al., 2008, Lum et al., 2009, Nowak, 2008, McCrea et al., 2002, Platz et al., 1999).

The focus of the systematic review reported here was to deepen understanding of the underlying mechanisms of reach-to-grasp by collating evidence of how kinematic characteristics are changed after stroke. It is expected that such knowledge may provide targets for improved upper limb rehabilitation techniques. There have been narrative reviews examining the biomechanics of reaching (McCrea et al., 2002), coordination and neural control of reach-to grasp (van Vliet et al., 2013), kinematic analysis of the upper limb during reaching (Alt Murphy and Häger, 2015), and the kinematics and cortical correlates of grasping (Nowak, 2008). However, the kinematic characteristics of reach-to-grasp have not yet been synthesized in a systematic review.

To address the first research question within the thesis this systematic review aims to (1) determine if kinematic characteristics such as movement time, peak velocity, trunk contribution, smoothness of movement, reach path ratio, and elbow range of motion are different in stroke survivors compared neurologically intact adults through meta-analysis (where possible); and (2) determine the influence of task requirements such as object location, upper limb motor impairment, trunk restraint, and movement speed on reach-to-grasp kinematics through meta-analysis.

3.2 Methods

The methods of this systematic review are based on the guidelines by the Cochrane Collaboration (Higgins et al., 2008). The protocol for this systematic review can be found on the Prospero database, registration number: CRD42014009479. Decisions about inclusion of studies, assessment of potential risk of bias, and extraction of data were made by two reviewers working independently. The two independent reviewers compared their results for consistency at every stage. For any disagreements the two reviewers met and referred to the source documents. If agreement could not be reached then a third researcher was consulted.

3.2.1 Search strategy

The search strategy was formulated in collaboration with a research librarian. The search terms include those related to the upper limb, reach to grasp, kinematics, biomechanics, electromyography, transcranial magnetic stimulation (TMS), and movement analysis; an example of the search strategy used in MEDLINE can be found in Table 6. The search strategy was modified for each electronic database based on specific MESH terms within the database. The databases searched were: MEDLINE, AMED, and Embase. Additionally, the reference lists of relevant papers were hand searched for relevant titles that were not captured in the database search. The data bases were searched from their inception MEDLINE in 1946, AMED in 1986, and Embase in 1974. The first search was completed on 11 April 2013 and the final search was completed on 20 January 2015. The search was limited to articles published in the English language.

Table 6 - Search Strategy used in Medline

1. Upper extremity OR arm OR hand
2. (upper limb).tw
3. Stroke.tw
4. “range of motion, articular”/ph
5. Movement/ph
6. Muscle, skeletal/ph
7. Motor skills/ph
8. arm/ph
9. Exp Muscle contraction (includes isotonic contraction, isometric contraction and excitation contraction coupling)
10. (muscle activation OR co?contraction OR motor control).tw
11. (grasp* OR reach* OR grip* OR pinch* OR limb transport).tw
12. Exp psychomotor performance (includes motor skills and performance analysis)
13. Electromyograph* OR transcranial magnetic stimulation OR biomechanics
14. (co?contraction OR EMG OR motor evoked potential OR biomechanic* OR electromyograph* or kinematic* OR object manipulation).tw
15. (1) OR (2)
16. (15)AND (3)
17. (4) OR (5) …OR (11)
18. (12) OR (13) OR (14)
19. (16) AND (17) AND (18)

Limits: individuals > 18 years of age; human; English Language

Tw=text word, ph=physiology

Table 6 The search strategy used to search the database MEDLINE. The database was searched from 1946 to 20 January 2015.

Table 7 Search Strategy used in the AMED Database

1. Upper extremity OR arm OR hand
2. (upper limb).tw
3. Stroke -map to subject heading (cerebral hemorrhage OR cerebral infarction OR cerebral ischemia OR cerebrovascular accident OR stroke]
4. Range of motion (map to subject heading)
5. Movement - map to subject heading > movement OR motor activity
6. Muscle, skeletal
7. Motor skills- map to subject heading > motor skills OR reaching
8. Exp muscle contraction (isometric contraction, isotonic contraction)
9. (muscle activation OR co?contraction OR motor control).tw
10. (grasp* OR reach* OR grip* OR pinch* OR limb transport).tw
11. Exp psychomotor performance (includes motor skills or reaching)
12. (task performance analysis).tw
13. Electromyograph* OR transcranial magnetic stimulation OR biomechanics OR kinematics
14. (co?contraction OR EMG OR motor evoked potential OR kinematic* biomechanic* OR electromyograph* OR object manipulation).tw
15. (1) OR (2)
16. (15) AND 3
17. (4) OR (5) ….OR (10)
18. (11) OR (12) OR (13) OR (14)
19. (16) AND (17) AND (18)

Table 7 The search strategy used in the AMED database. The data base was searched from 1985 to 20 January 2015.

Table 8 Search strategy used in the Embase database

1. Arm OR hand
2. (upper extremity OR upper limb).tw
3. Stroke.tw
4. Exp “Range of motion” includes range of motion, articular and movement(physiology)
5. Movement (physiology) includes limb movement OR musculoskeletal function
6. Skeletal muscle > skeletal muscle or arm muscle or hand muscle
7. Motor performance
8. Muscle contraction
9. (muscle activation OR co?contraction OR motor control).tw
10. (grasp* OR reach* OR grip* OR pinch* OR limb transport).tw
11. Psychomotor performance includes psychomotor activity OR task performance
12. Electromyograph* OR transcranial magnetic stimulation OR biomechanics
13. (co?contraction OR EMG OR motor evoked potential OR kinematic* biomechanic* OR electromyograph* OR object manipulation OR motor skills).tw
14. (1) OR (2)
15. (14) AND (3)
16. (4) OR ….(10)
17. (11) OR (12) OR (13)
18. (16) AND (17) AND (18)

Table 8 The search strategy used to search the Embase database. The database was searched from 1974 to 20 January 2015.

3.2.2 **Types of studies**

Studies in which both the stroke and control participants completed identical reach-to-grasp tasks were considered for inclusion in this review. Single case study designs were excluded.

3.2.3 **Types of participants**

Participants included in potential studies had to be at least 18 years of age and have had a stroke. There were no limitations placed on stroke location, time since stroke or number of strokes. The control participants had to have no neurological or musculoskeletal disorder.

3.2.4 **Types of reach-to-grasp tasks**

The study had to assess reach-to-grasp and lift, or reach-to-grasp and transport of an object. Specific exclusion criteria includes: reach to a target, pointing, tracing, and drawing tasks.

3.2.5 **Types of outcome measures**

The outcomes assessed had to be a kinematic measure e.g. velocity, smoothness, arm trajectory; or an electromyography (EMG) measure e.g. muscle activation patterns, muscle synergies, or a measure of corticospinal excitability e.g. motor evoked potential. The same outcomes had to be measured in both the stroke survivors and controls within each study.

3.2.6 **Identification of relevant studies**

Two reviewers independently assessed potential studies for relevance based on the pre-specified study criteria described in Table 9. Studies were assessed as not relevant, probably relevant, and relevant. Title and abstract were screened together. Then those potential studies deemed relevant or probably relevant underwent full text screening (Mateen et al., 2013, Higgins et al., 2008).

Table 9 - Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Assess reach to grasp using the contra-lesional limb via motion analysis, EMG, or TMS	Robot-assisted reaching Reaching against a load Reach with the Ipsilesional limb
2. Reaching task must involve reach to grasp of an object, reach to grasp and lift, or reach to grasp and transport of an object Reach defined as transport of the hand across a distance	A task involving reach/point to a target, tapping movement, drawing movement, tracking movement, scaling of grip force, or assessment of torque
3. Study includes healthy adults and stroke survivors who complete the same reach-to-grasp task	
4. Assess level arm motor ability of the contra-lesional upper limb using a clinical measure for example the Action Research Arm Test (ARAT), Fugl-Meyer, or Wolf Motor Function Test	
5. Participants aged > 18 years of age	
6. Study design that includes comparison between stroke survivor and healthy control	Single case study design

Table 9 Inclusion and exclusion criteria utilised to identify relevant primary studies for inclusion in the review. The criteria were used at title and abstract stage and full text stage.

3.2.7 **Potential risk of bias**

One of the strengths of a systematic review compared to a narrative review is assessing the methodological quality or potential risk of bias of included studies (Higgins et al., 2008). A systematic review of studies of lower potential risk of bias can ensure confidence in the results. Methodological quality can refer to study design that protects against bias such as systematic, non-systematic or inferential error (Mallen et al., 2006). There are a variety of tools available to assess the potential risk of bias and methodological quality of studies. For example some tools are designed specifically for randomized controlled trials (RCT) such as the Cochrane Collaboration tool (Higgins et al., 2008) Jadad Scale, and the PEDro Scale (Olivo et al., 2008). The studies included in this review were mostly of observational design. Therefore, the Down's and Black Tool was used in this review as it is applicable to both RCT and non-RCT studies (Downs and Black, 1998). The Down's and Black tool has documented validity, inter-rater, and test-retest reliability (Downs and Black, 1998). Furthermore, The Down's and Black Tool has been used in previous systematic reviews of observational studies with modifications to be applicable to the individual reviews (Gorber et al., 2007, Monteiro and Victora, 2005). The Down's and Black Tool was modified to be applicable to the studies in this systematic review based on core criteria pertinent to assess methodological quality such as internal validity (study design, conduct, and analysis), and external validity (sample, generalizability) (Higgins et al., 2008, Mallen et al., 2006). Example modifications made were removing questions relating to group concealment and allocation as that is specific to RCT's. Blinding of participants was not removed from the Down's and Black tool. Blinding is a key aspect to study design and potential bias. Observational study design falls lower on the hierarchy of studies due to the lack of blinding (Higgins et al 2008). The studies included in the systematic review were mainly of one session assessments and blinding participants to the activity was not possible. Despite the impossibility of blinding it is a feature that places observational studies lower than RCT's, can induce bias, and can be a confounder thus is important to incorporate into the review. The Down's and Black tool with the modifications and rationale for modifications is in Appendix 1; the final tool used for assessment of potential risk of bias is shown in Appendix 2.

The original Down's and Black Tool was scored as yes (the paper fulfilled the question) no, (the paper did not fulfil the question), or unclear/partially (unable to determine if the paper fulfilled the question); points were assigned to each answer yes=1-2, unclear/partially =0-1 and no =0. As the tool was modified a number score was not assigned. Questions were answered low risk (the paper fulfilled the question), unclear risk (unable to determine if the paper fulfilled the question or insufficient evidence) and high risk (the paper did not fulfil the

question). Additionally, items were not weighted as there is a lack of empirical basis to give weights to the questions or domains; weighting of items can induce bias into the findings (Greenland and Morgenstern, 2001).

3.2.8 **Data extraction**

Data extracted include: number of participants, age, and time since stroke, reach-to-grasp task, trunk restraint, upper limb motor ability, and kinematic characteristics (e.g. velocity). For studies in which the data were unclear, the authors were emailed requesting the relevant data. In studies involving an intervention, only the baseline data was extracted for both stroke and control participants to exclude any influence of the intervention on reach-to-grasp.

3.2.9 **Synthesis and interpretation**

Where meta-analysis was indicated it was conducted using the Cochrane Statistical package RevMan 5.2. If meta-analysis was not indicated a narrative synthesis was planned to further describe the kinematic differences between stroke survivors and healthy control participants.

As data were continuous the meta-analysis was undertaken using the standardized mean difference of kinematic characteristics between stroke survivors and control participants (Higgins et al., 2008). Where possible, subgroups were formed based on specific task requirement such as object location in the workspace. To determine if a fixed-effect or random effects model was appropriate heterogeneity of data was assessed. Heterogeneity of data was assessed using the I^2 statistic and interpreted such that an I^2 value of < 25% was low, 50% moderate, and 70% was high heterogeneity. If I^2 was < 25% a fixed effect model was used, if not a random effects model was used (Higgins et al., 2008).

Where more than one reach-to-grasp task was included within the same study, with the same individuals, then each separate task was included in the meta-analysis and the participants were divided among the tasks to ensure that each individual only counted once in the analysis. For example, if a study included three reaching tasks, with n=9 in the control and n= 9 in the stroke group then three control and three stroke participants would have been included in each of the three tasks in the meta-analysis (Higgins et al., 2008). In the case of multiple tasks within one study, participants were equally divided between the tasks to prevent bias in the findings. If there were an odd number of participants, such as seven participants and two tasks, three would have been allocated to one task and four to another.

The participants included in this review had varied level of upper limb function from mild motor deficits to moderate-severe motor deficits, and a range in time since stroke from 2 days to 9.4 years. Sensitivity analysis was used to assess the robustness of the results of

the meta-analysis based on severity of paresis and time since stroke (Chang et al., 2004, Higgins et al., 2008).

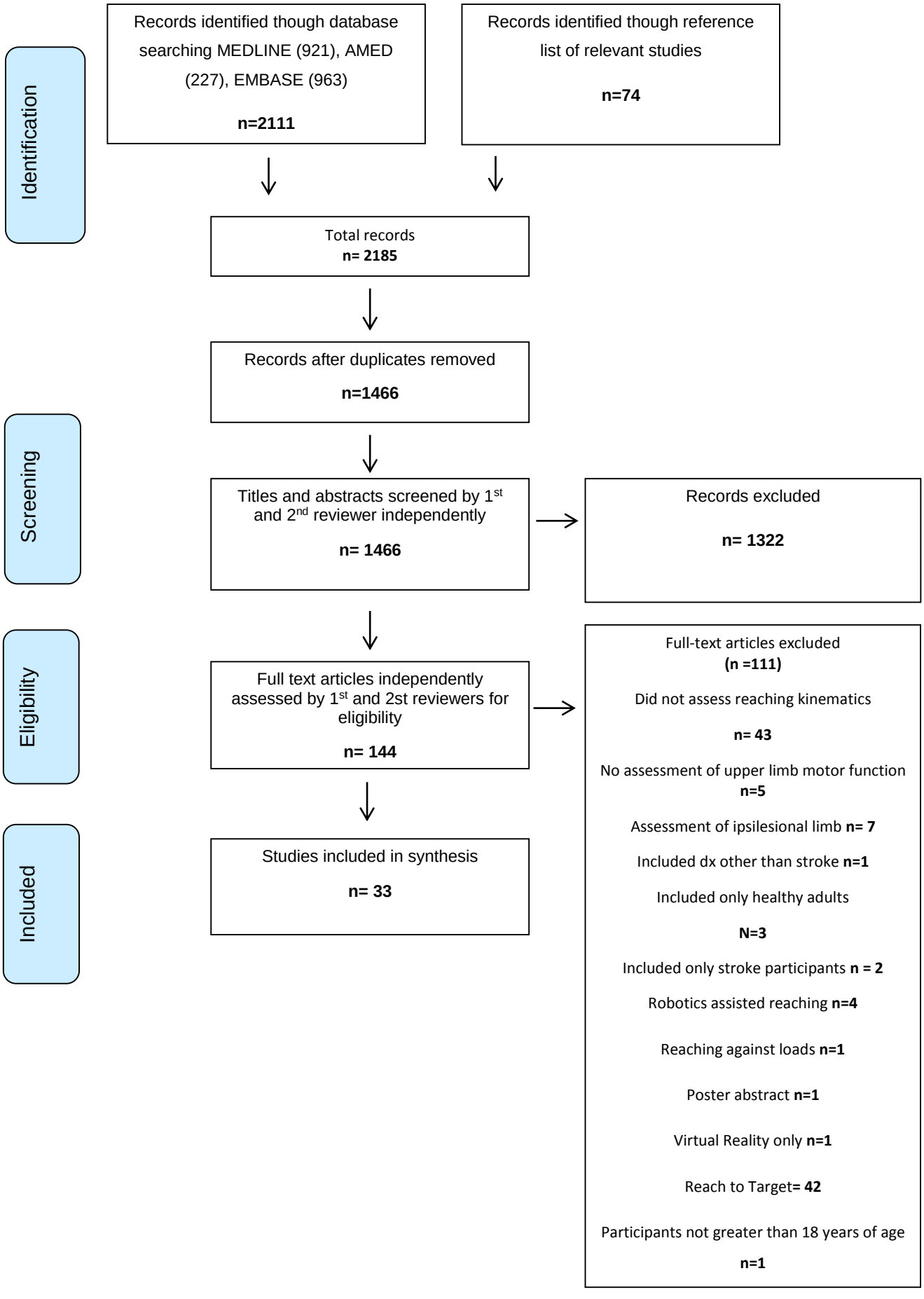
The meta-analysis was interpreted with regard to the potential risk of bias of the individual studies.

3.3 Results

3.3.1 Relevant studies

The electronic database search identified 2,111 potential references, and a further 74 references were identified from the reference list of relevant papers. Of these 2,185 references, 33 studies met the inclusion and exclusion criteria. Full details are provided in the PRISMA flowchart (Figure 5).

Figure 5 - PRISMA Diagram



3.3.2 **Description of studies**

No articles were identified that utilized TMS during reaching. One article was identified that utilized EMG so there was not a comparison study. Therefore, the remainder of the reported review refers only to kinematic characteristics.

3.3.3 **Participants**

Reach-to-grasp was assessed with 488 participants with stroke, and 350 healthy control participants. The participant characteristics for each study can be found in Table 10 and Table 11, at the end of this chapter. The age of the participants with stroke ranged from 24-94 years of age; with mean age and standard deviation being 60.23±7.3 years; the healthy control participants age range was 22-87 years and mean age and standard deviation was 55.8±9.2 years. The mean time of assessment post stroke was 865.54 days (2.37 years) with a range of 2 days to 9.4 years post stroke across included studies. The stroke participants were reported to have a range of upper limb motor function categorised from mild to severe. In studies published by the same authors it is possible that the same participants were involved in multiple studies. For example, Dejong et al. (2012 A) and Dejong et al. (2012 B) have one participant different in the stroke group, Roby Brami et al. (2003 A) and Roby-Brami et al. (2003 B) may have used the same control group, and Levin et al. (2002) and Michaelsen et al. (2001) the peak velocity and movement time share the same mean and standard deviation for two reaching tasks. Where there was thought to be overlapping participants, the meta-analysis was conducted with and without the studies under question. Neurologically intact control participants were not consistently age matched to the stroke participants in included studies.

3.3.4 **Reach-to-grasp task**

The reach-to-grasp tasks varied across studies. Full details can be found in Table 10 and Table 11. The variation in tasks were: reach and grasp e.g. (Michaelsen et al., 2004, Patterson et al., 2011); reach and lift of an object e.g. (Chang et al., 2008, Dejong and Lang, 2012); reach-to-grasp and transport of an object e.g. (Alt Murphy et al., 2011, Aruin, 2005); object location (central vs ipsilateral workspace); reaching speed (self-selected vs fast speeds); trunk restrained or unrestrained; movement initiation to a cue or self-directed; and assessment of the dominant and non-dominant limbs of the control participants. Authors of multiple studies utilised the same or a similar task across their own studies.

3.3.5 **Outcome measures**

Motor function of the upper limb of stroke participants was assessed using a variety of observational clinical assessments. A few examples are the Fugl-Meyer Motor Assessment; Chedoke McMaster Stroke Assessment Scale; and the Functional Independence Measure.

The diversity in assessment creates difficulty for comparisons between participants' functional ability.

Similar to motor function, methods of data collection, data processing and analysis of kinematic characteristics investigated varied across studies. The most common kinematic characteristics measured were: movement time, velocity, movement smoothness, reach path ratio/trajectory, range of motion, and trunk contribution to reaching.

Table 10- Reach-to-Grasp Studies in the Ipsilateral Workspace

Study	Participants	Time Since Stroke	Reach-to-Grasp Task			Object Placement	Movement Speed			Trunk Restraint
			Grasp	Grasp and Lift	Grasp and Transport		Self-Selected	Fast	Not Reported	
Aruin et al. 2005	**S:** 6; Age: 67.6, ±15.8 **C:** 6; Age: 64.7±18.8	20.8±6.6 days			√	Final object placement was 0.25m from start	√			Not reported
Chang et al. 2008	**S:** 17; Age: 60.7 (28-86) **C:** 17; Age: 61.9 (35-87)	> 6 months		√		A distance the length of the arm	√			Yes
DeJong et al. 2012 A	**S:** 16; Age: 58±11 (33-88) **C:** 12; Age: 53.0±15.8 (32-81)	1.2±2.7 (0.04-9.2) years		√		90% of arm's length	√			Not reported
De Jong et al. 2012 B	**S:** 16; Age: 59±11(39-88) **C:** 11; Age: 55±15(34-81)	1.2 months (2 weeks to 9.4 years)		√		90% of arm's length	√			Not reported
Kilbreath et al. 2006	S: 13; Age 67.9(8.3) 55-77 C: 13; Age 69.6(9.9) 57-86	36.1±18.0 months			√	150mm to grasp the tray and final position located an additional 110 mm	√			Yes

Study	Participants	Time Since Stroke	Reach-to-Grasp Task			Object Placement	Movement Speed			Trunk Restraint
			Grasp	Grasp and Lift	Grasp and Transport		Self-Selected	Fast	Not Reported	
Lang et al. 2005	**S:** 39; Age: 65.0±13.4 (39-94) **C:** 10; Age: 59.1±12.5	9.6±4.5 days (2-25)			√	90% of arm's length			√	Yes
Lum et al. 2009	**S:** 4; Age not reported **C:** 3; Age not reported	1-3 months			√	Not reported	√			Not reported
Nowak et al. 2007	**S:** 16; Age: 55 (24-85) (R stroke: 58±17; L stroke: 51±16 **C:** 8; Age: 56±17	1-8 months		√		30 cm from start position	√			Not reported
Patterson et al. 2011	**S:** 18; Age: 67.6±8.1 **C:** 9; Age: 57.2±6.7	7 -174 months	√			80% of arm's length	√			No (backless chair)
Raghavan et al. 2010	**S:** 8; Age: 27-79 **C:** 8; Age: ±2 years of the stroke participants	3-109 months		√		75% of arm's length			√	Not reported

Study	Participants	Time Since Stroke	Reach-to-Grasp Task			Object Placement	Movement Speed			Trunk Restraint
			Grasp	Grasp and Lift	Grasp and Transport		Self-Selected	Fast	Not Reported	
Sangole et al. 2009	**S:** 10; Age 65±9 (51-79) **C:** 8; Age: 55±10 (41-68)	1.4-9 years			√	90% of arm's length then transferred object medially	√			Not reported
Silva et al. 2014	**S:** 9; Age: 55.0±9.6 **C:** 9; Age: 52.3(Van Kordelaar et al., 2012, van et al., 2012)±4.9	1-8 years	√			Anatomical reaching distance			√	No
Van-Kordelaar et al. 2012 A	**S:** 46; Age 60.30±12.59 **C:** 12; Age 52.75±5.88	mild group: 6.4±2.2 years, moderate-severe group: 6.1±4.3 years			√	Not reported	√			No
Van Kordelaar et al. 2012 B	**S:** 1; Age: 41 **C:** 1; Age 43				√	Maximal reaching distance	√			No
Van Kordelaar et al. 2013	**S:** 31; Age: 60.0 ±11.2 **C:** 12; Age: 52.8±5.9	Serial measurements (weeks) M1 14±6 M2 25± M3 38±5 M4 57±10 M5 92±14 M6 189±11			√	Not reported	√			No

Study	Participants	Time Since Stroke	Reach-to-Grasp Task			Object Placement	Movement Speed			Trunk Restraint
			Grasp	Grasp and Lift	Grasp and Transport		Self-Selected	Fast	Not Reported	
Van Vliet et al. 2007	**S:** 12 ; Age: mean 66.9 **C:** 12; Age: mean 64.8	3-113 weeks	√			20 cm anterior to start position			√	Not reported
Van Vliet et al. 2009	**S:** 9; Age: 71.4 (41-89) **C:** 9; Age: 68.5	0.5-22 weeks			√	8 cm, 13 cm and 18 cm from start position of the hand			√	No
Viau et al. 2004	**S:** 7; Age: 48.9±18.6 **C:** 8; Age: 56.8±17.1	43.7±15.3 months			√	13 cm anterior to the hand, final position 31 cm in front of shoulder, 12.5 cm above and 14 cm to the right of the initial ball position			√	Not reported
Wenzelburger et al. 2005	**S:** 18; Age: 60.9 ±10.7 (40-81) **C:** 18; Age (mean) 62	2.4 ±1.9 years		√	√	34 cm above the table and 50 cm from the body	√			Not reported
Wu et al. 2000	**S:** 14; Age: 61.79 (39-84) **C:** 25; Age: 63.80 (37-81)	5-174.5 months			√	16.5 cm			√	Not reported

Table 10Table 10 Summary of characteristics of individual studies in which reach-to-grasp occurred in the ipsilateral workspace. Summary of participants, time since stroke, reach to grasp task (grasp, grasp and lift, or grasp and transport, object distance, movement speed, and if trunk restraint was used during the task.

Table 11 - Reach to-Grasp studies in the Central Workspace

Study	Participants	Time Since Stroke	Reach-to-Grasp Task			Object Placement	Movement Speed			Trunk Restraint
			Grasp	Grasp and Lift	Grasp and Transport		Self-Selected	Fast	Not Reported	
Alt Murphy et al. 2011	**S:** 19; Age: 61±11.1 **C:** 19; Age: 57.3 (41-78)	18.9±16.4 (4-63) months			√	30 cm from edge of table	√			No
Aprile et al. 2014	**S:** 6; Age: 78 (64-84) **C:** 6; Age: 64.5 (52-74)	1-6 months			√	400 mm from edge of table	√			Not reported
Levin et al. 2002	**S:** 11; Age: 54.8±13.9 **C:** 11; Age: 55.0±13.7	5-72 months			√	4 locations: T1 ½ arm's length, T2 arm's length, T3 1 & 1/3 arm's length, T4 2x arm's length	√			No
Messier et al. 2006	**S:** 15; Age: 69.4±12.0 **C:** 15; Age: 69.4±12.0	3-132 months			√	Distal target was 20 cm from initial cone position	√			Not reported
Michaelsen et al. 2004	**S:** 19; Age: 52±19 **C:** 7; Age: 53±24	31±22 (6-82) months	√			90% of arm's length	√			No
Michaelsen et al. 2001	**S:** 11; Age: 54.8±13.9 **C:** 11; Age: 55.0±13.7	5-69 months	√			2 locations: T1 ½ arm's length, T2: arm's length	√			Trials with and without trunk restraint?
Roby-Brami et al. 2003 A	**S:** 15; Age: 55.8 (36-69) **C:** 7; Age: 35.8 (22-53)	confusing p 370; 9-153 days; or maybe 24-224 days (time of functional			√	One of 7 locations in a 20 x 20 cm board (25-45 cm in front of participant) the far targets were just beyond arm's reach	√			Not reported

Study	Participants	Time Since Stroke	Reach-to-Grasp Task			Object Placement	Movement Speed			Trunk Restraint
			Grasp	Grasp and Lift	Grasp and Transport		Self-Selected	Fast	Not Reported	
		assessment p 371)								
Roby-Brami et al. 2003 B	**S:** 8; Age: 55.7 (36-68) **C:** 7; Age: 35.8 (22-53)	48-153 days			√	One of 7 locations in a 20x20 cm board, the far locations were 103-121% of arm's length			√	Not reported
Roby-Brami et al. 1997	**S:** 17; Age: 51.2 (35-75) **C:** 6; Age: 51.8 (41-58)	1-18 months			√	One of six locations in a wooden board about 15 cm from abdomen	√			Not reported
Schaefer et al. 2012	**S:** 16; Age: 58±11 **C:** 12; Age: 53±16	657±1287 days		√		90% of arm's length	√			Not reported
Van Dokkum et al. 2013	**S:** 13; Age 63.9±9.4 **C:** 12; Age: 32.5±11.4	13-30 days			√	Initial positon 20 cm anterior to participant end position 5 cm from edge of table	√			Yes
Wu et al. 2009	**S:** 14; Age: 60.0±9.1 **C:** 13; Age: 59.1±10.6	23.0±26.7 (2.3-78.6) months			√	Initial position 80% of arm's length, end location 1/3 the distance of 80% of arm's length	√			Yes
Wu et al. 2008	**S:** 14; Age: 60.70±10.00 **C:** 13; Age: 59.14±10.59	31.23 (6.6-84) months			√	Initial position 80% of arm's length, end location 1/3 the distance of 80% of arm's length	√			Yes

Table 11 Summary of characteristics of individual studies in which reach-to-grasp occurred in the central workspace. Summary of participants, time since stroke, reach to grasp task (grasp, grasp and lift, or grasp and transport, object distance, movement speed, and if trunk restraint was used during the task.

Table 12 - Summary of studies included

Ipsilateral Workspace

Movement Speed	Grasp	Grasp and Lift	Grasp and Transport
Self-Selected	I	4	8
Fast Speeds	0	0	0
Speed Not Reported	2	0	4

Central Workspace

Movement Speed	Grasp	Grasp and Lift	Grasp and Transport
Self-selected	2	1	9
Fast Speeds	0	0	0
Speed not reported	0	0	1

Table 12 - Summary of studies included in the systematic review based on type of task: grasp, grasp and lift, grasp and transport, speed: self-selected or fast, and area of the workspace. A majority of studies included tasks at self-selected speeds and grasp and transport of objects.

3.3.6 **Potential risk of bias**

All of the studies included were assessed as having unclear or high potential risk of bias. The full details of the potential risk of bias are provided in Table 13. The areas in which potential risk of bias were most evident were in the: in the reporting of adverse events; reporting of attrition; blinding of participants; and blinding of assessors. Of great importance for this review the reproducibility of the reach-to-grasp task for study replication and the description of stroke survivors for sufficient interpretation of the findings and generalizability. The blinding of assessors is also important as this can induce bias in the results. Of less importance is the blinding of participants; participants were not able to be blinded as they were participating in the reach-to-grasp activity. Studies with higher potential risk of bias are therefore those in which the reach-to-grasp task was not reproducible, or the stroke survivors were not adequately described limiting the interpretation and generalizability of the findings. The studies with lower potential risk of bias had insufficient information regarding reporting of adverse events, attrition, or lack of blinding. Four studies demonstrated unclear or high potential risk of bias in reproducibility of the reach-to-grasp task and description of participant characteristics (Aprile et al., 2014, Chang et al., 2008, Wu et al., 2000, Lum et al., 2009).

A sensitivity analysis was not conducted based on potential risk of bias of included studies. Threshold for high potential risk of bias is arbitrary and could induce bias into the findings; alternatively not including all studies in the analysis may contribute to imprecise findings (Higgins et al., 2008). There were four studies in which higher potential risk of bias was present in reproducibility of reach-to-grasp task and description of stroke survivors. The only common kinematic outcome assessed by three of the four studies was movement time; aside from movement time the studies measured different outcomes. The findings of the three studies with higher potential risk of bias are line with the findings of the studies of lower potential risk of bias as demonstrated by the forest plots (mean difference on the same side of the line of no difference and similar confidence intervals (Higgins et al., 2008).

Table 13 - Potential Risk of Bias of Included Studies

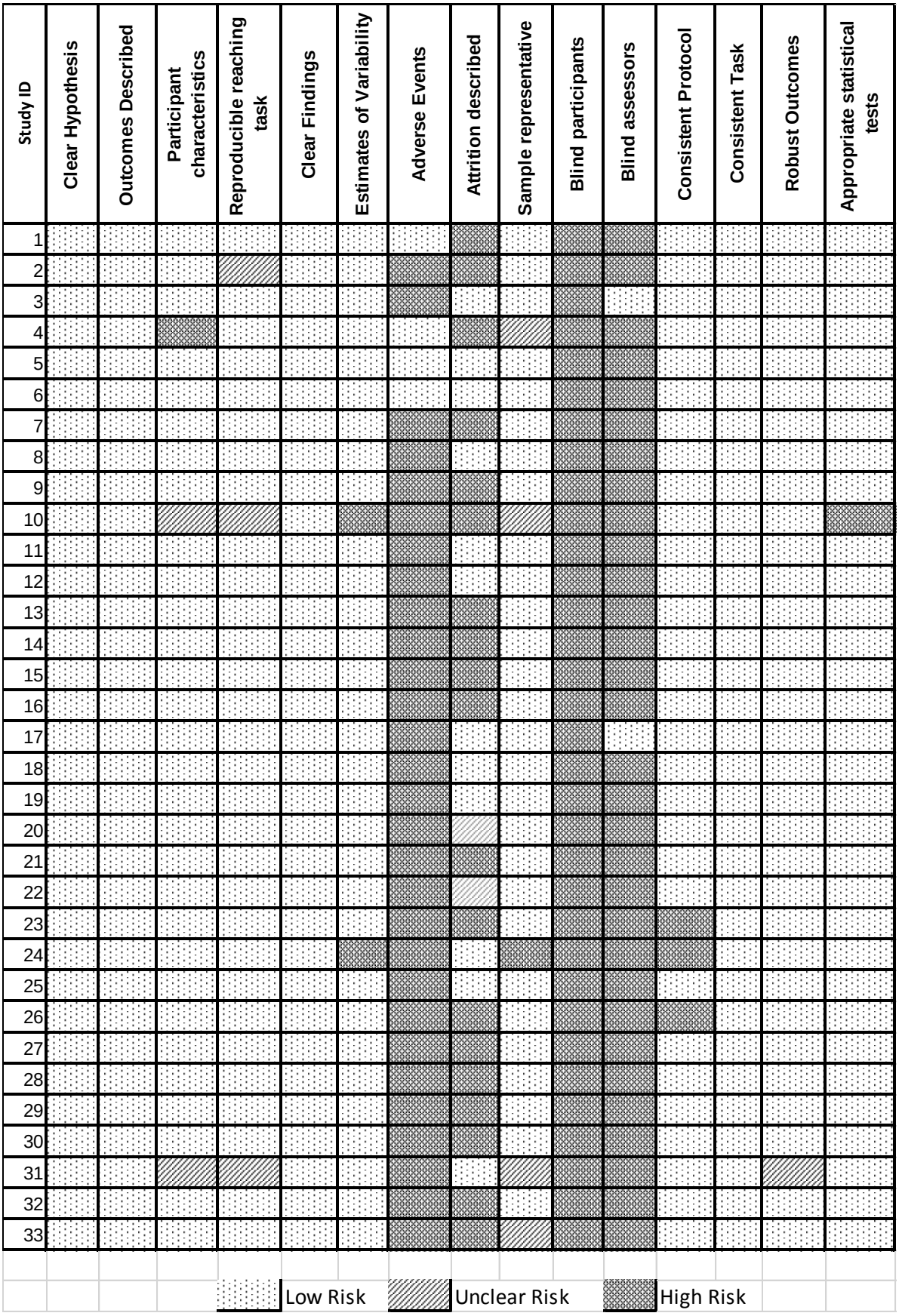


Table 13 - Potential Risk of Bias of Included Studies. The potential risk of bias was assessed using the modified Down's and Black Tool in Appendix 2: Modified Downs and Black Tool - for Assessment of Potential Risk of Bias. All studies exhibit unclear or high potential risk of bias.

3.3.7 Synthesis

3.3.7.1 Meta-analysis

Data were sufficiently similar to undertake a meta-analysis for: peak velocity; movement time; reach path ratio (trajectory); trunk displacement; movement smoothness; and elbow range of motion. Meta-analysis used the standardized mean difference between stroke survivors and neurologically intact control participants.

3.3.7.2 Research Aim 1a: Determine the differences in kinematic characteristics between stroke survivors and neurologically intact adults during reach to grasp

The findings of the meta-analyses are summarised in Table 14 the Forest Plots are in Figure 6 through Figure 17. Based on the I^2 statistic heterogeneity was low < 25% for peak velocity (ipsilateral workspace), reach path ratio (central workspace), trunk displacement (ipsilateral workspace), smoothness of movement (central workspace); heterogeneity was moderate to high for all other meta-analyses I^2 > 25%. Eleven meta-analyses were completed the individual forest plots are in Figure 6 through Figure 17. Stroke survivors' kinematic characteristics were found to be significantly different from control participants in nine of the eleven meta-analyses. Stroke participants demonstrated significantly: lower peak velocity (SMD and 95% CI) central: -1.48(-1.94, -1.02), ipsilateral: -1.41 (-1.75, -1.08); longer movement time central: 1.97 (1.23, 2.72), ipsilateral: 1.66 (1.22, 2.09); greater trunk displacement central: 1.55 (0.85, 2.25), ipsilateral: 1.58 (0.88, 2.27); decreased smoothness central: 1.81 (1.19, 2.43); less elbow extension -0.94 (-1.80, -0.08); and a more curved reach path ratio ipsilateral: 1.68 (1.22, 2.13). The other meta-analyses were not significant reach path ration central: 0.57 (-0.09, 1.23); smoothness of movement ipsilateral: 0.65 (-0.54, 1.85). There was moderate to high heterogeneity (I^2 > 25%) six of eleven meta-analyses, and there was unclear or high potential risk of bias for all studies; thus the findings of the meta-analyses should be interpreted with caution.

3.3.7.3 Research Aim 1b: Determine the influence of task requirements, upper limb paresis and time since stroke on kinematic characteristics, meta-analysis

Meta-analyses investigating kinematic differences based on object location identified, significant differences in kinematics in all but two meta-analyses. The non-significant differences between stroke survivors' kinematics and neurologically intact controls were in were reach path ratio in the central workspace, and smoothness of movement in the ipsilateral workspace. The other meta-analyses in the central and ipsilateral workspace were all significant (peak velocity, movement time, reach path ratio, trunk contribution, smoothness of movement and elbow extension). There were no significant differences between meta-analyses when reaching in the ipsilateral or central workspace.

Insufficient data was provided to complete a meta-analysis investigating the influence of trunk restraint and movement speed on kinematics.

Sensitivity analyses were completed on upper limb motor impairment, and time since stroke. There were no differences in findings of the meta-analyses when excluding studies that included mild stroke, moderate stroke or participants who were less than three months after stroke.

Table 14 - Summary of Meta-Analyses

Kinematic Characteristic Examined	Number of Participants	SMD [95% CI]	Stroke Survivors compared to Neurologically Intact Controls
Peak Velocity Central Workspace (all participants)	Stroke=106 Control=75	-1.4 [-1.94, -1.02]	↓
Peak Velocity Ipsilateral Workspace	Stroke=143 Control=80	-1.41 [-1.75, -1.08]	↓
Movement Time Central Workspace	Stroke=143 Control=80	1.97 [1.23, 2.72]	↑
Movement time Ipsilateral workspace	Stroke=240 Control=162	1.68 [1.22, 2.13]	↑
Reach Path Ratio Central Workspace (all participants)	Stroke=22 Control=22	0.57 [-0.09, 1.23]	=
Reach Path Ratio Ipsilateral Workspace	Stroke=110 Control=64	1.79 [1.06, 2.52]	↑
Trunk Contribution Central Workspace	Stroke=72 Control=52	1.55 [0.85, 2.25]	↑
Trunk Contribution Ipsilateral Workspace	Stroke=37 Control=16	1.58 [0.88, 2.27]	↑
Smoothness of Movement Central Workspace	Stroke=36 Control=36	1.81 [1.19, 2.43]	↓
Smoothness of Movement Ipsilateral Workspace	Stroke=31 Control=30	0.65 [-0.54, 1.85]	=
Elbow Range of Motion	Stroke=79 Control=70	-0.94 [-1.80, -0.08]	↓

Table 14 - Summary of the meta-analysis: standardised mean difference (SMD) and 95% CI, number of participants included in the meta-analysis, outcome of meta-analysis of kinematic characteristics comparing stroke survivors and neurologically intact participants reaching in the central and ipsilateral workspace. A fixed effect model was used if $I^2 < 25\%$, and a random effects model was used if $I^2 > 25\ \%$. The fourth column describes the outcome of the meta-analysis of kinematic characteristics comparing stroke survivors to neurologically intact control participants. Twometa-analyses demonstrated non-significant findings, reach path ratio in the central workspace, and smoothness of movement in the ipsilateral workspace.

Figure 6 - Forest Plots of Peak Velocity

*Figure 6*A

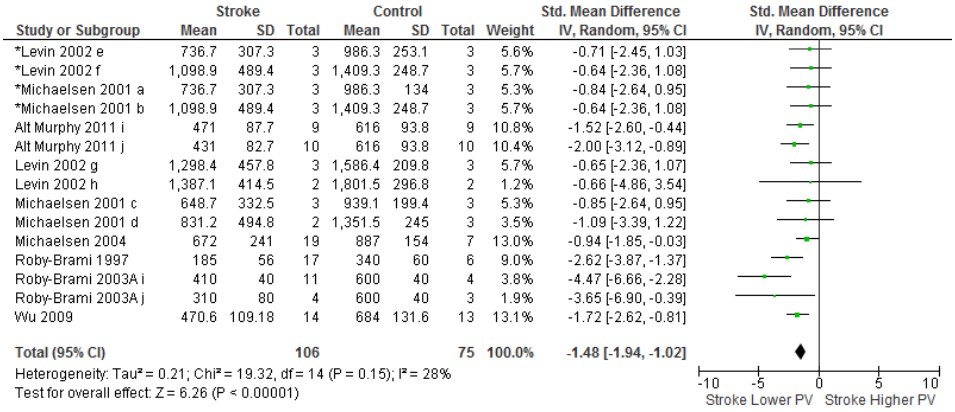


Figure 6A. SMD of peak velocity in the central workspace, all studies

*Figure 6*B

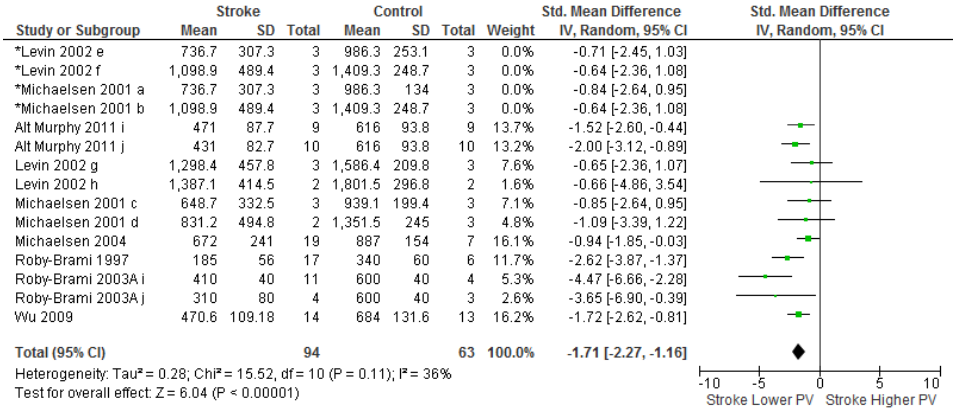


Figure 6B. SMD of peak velocity in the central workspace, excluding potentially overlapping participants

*Figure 6*C

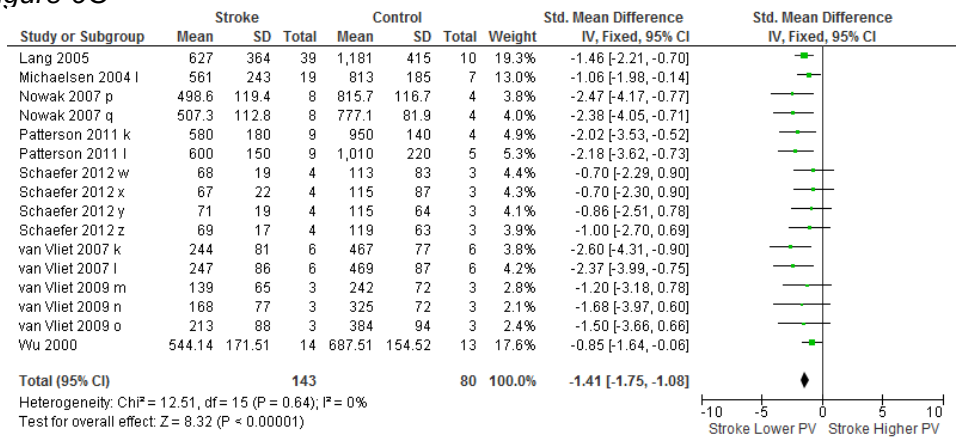


Figure 6C. SMD of peak velocity in the ipsilateral workspace

Figure 6A, B, C - Meta-analyses of standardised mean difference (SMD) comparing peak velocity of stroke survivors to neurologically intact control participants reaching in the central and ipsilateral workspace; Studies with an * indicate potentially overlapping participants. A fixed effects model was used if I^2 <25%, random effects model if I^2 > 25 %. The left side of the forest plot indicates lower peak velocity; the right side indicate higher peak velocity. Stroke survivors demonstrate significantly lower peak velocity. SMD=standardised mean difference

Figure 7 - Sensitivity Analysis of Peak Velocity

*Figure 7***A**

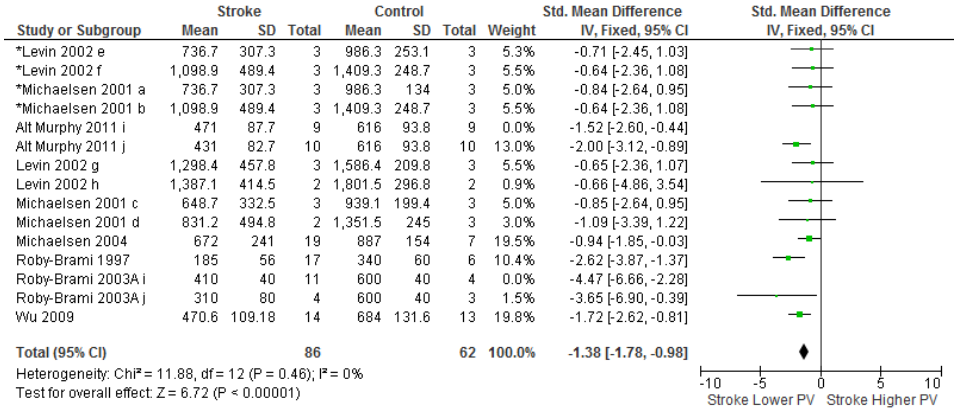


Figure 7 A. Sensitivity analysis of peak velocity excluding participants with mild stroke

*Figure 7***B**

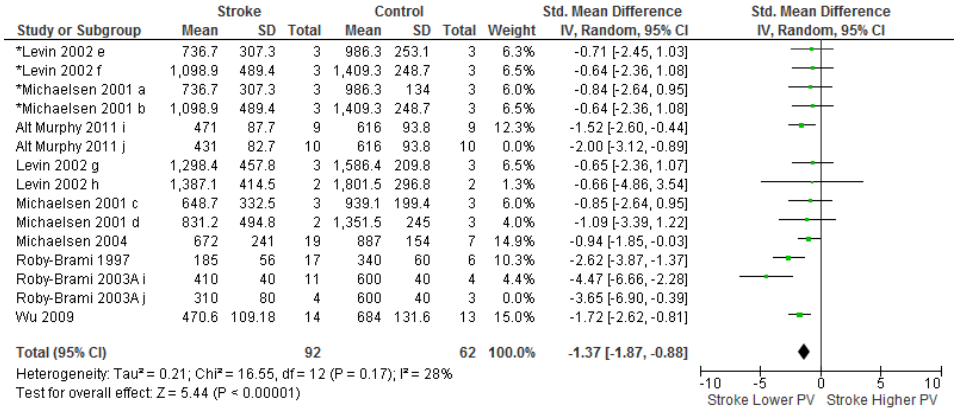


Figure 7 B. Sensitivity analysis of peak velocity excluding participants with moderate stroke

*Figure 7***C**

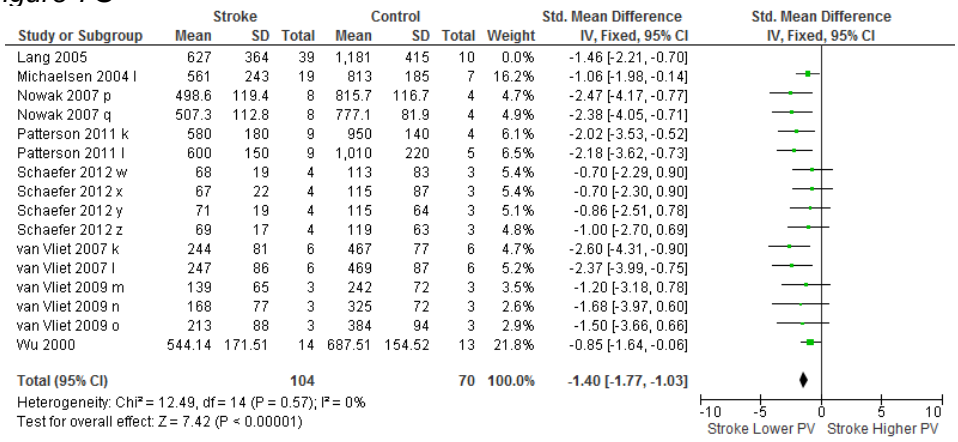


Figure 7C. Sensitivity analysis in the ipsilateral workspace excluding participants < 3 months after stroke

Figure 7A, B, C - Sensitivity analyses of the SMD comparing peak velocity of stroke survivors to neurologically intact control participants based on upper limb motor impairment and time since stroke respectively. A fixed model was used if $I^2 < 25\%$, and random effects if $I^2 > 25\%$. The left side of the forest plot indicates lower peak velocity; the right side indicates higher peak velocity. Studies with an * indicate potentially overlapping participants. Stroke survivors demonstrate significantly lower peak velocity. SMD=standardised mean difference

Figure 8 - Forest Plot of Movement Time

*Figure 8***A**

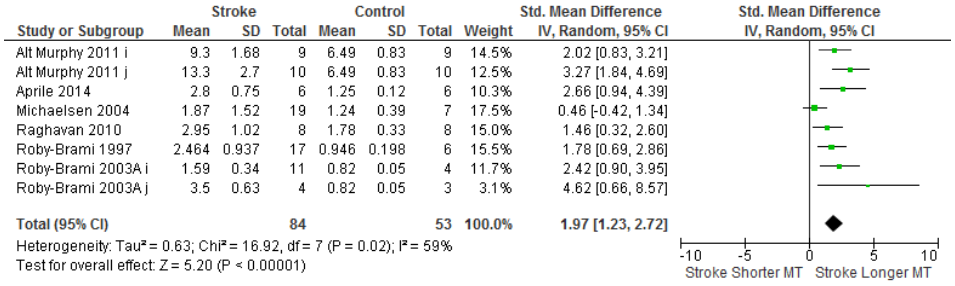


Figure 8A. SMD of movement time in the central workspace

*Figure 8***B**

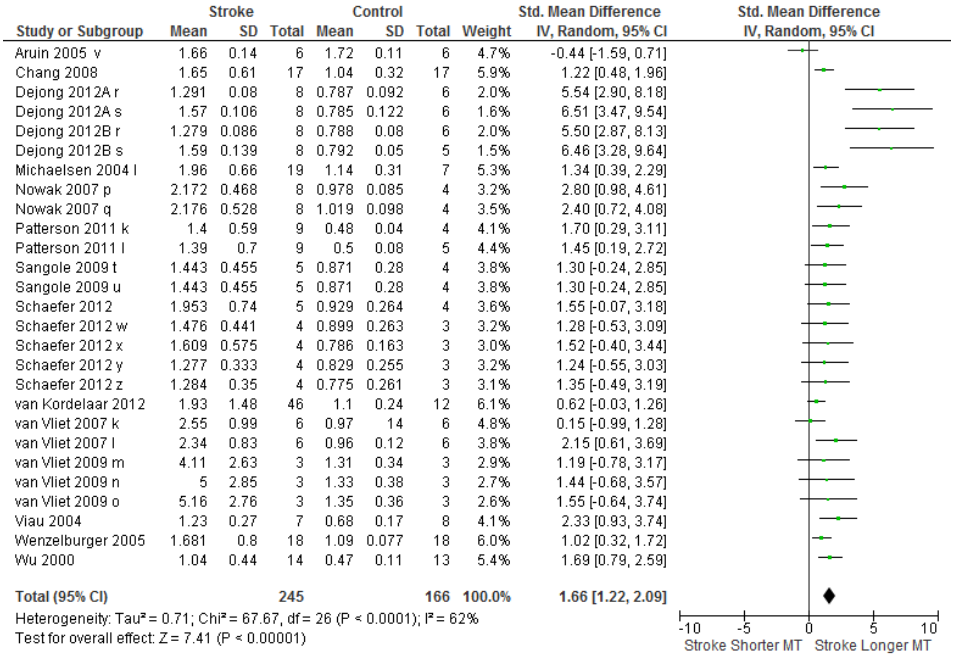


Figure 8B. SMD of movement time in the ipsilateral workspace

Figure 8A, B - Forest Plots of the SMD of movement time during reach-to-grasp comparing stroke survivors to neurologically intact control participants. A fixed effects model was used if $I^2 < 25\%$, a random effects model was used if $I^2 > 25\%$. The left side of the forest plot indicates shorter movement time, the right side of the plot indicates longer movement time. Stroke survivors demonstrate significantly longer movement times during reach-to-grasp in both the central and ipsilateral workspace. SMD=standardised mean difference

Figure 9 - Sensitivity Analyses Movement Time

Figure 9A

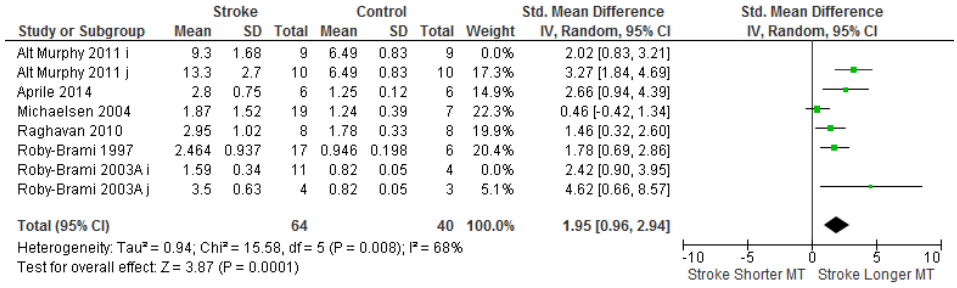


Figure 9A. SMD of MT in the central workspace excluding participants with mild stroke

Figure 9B

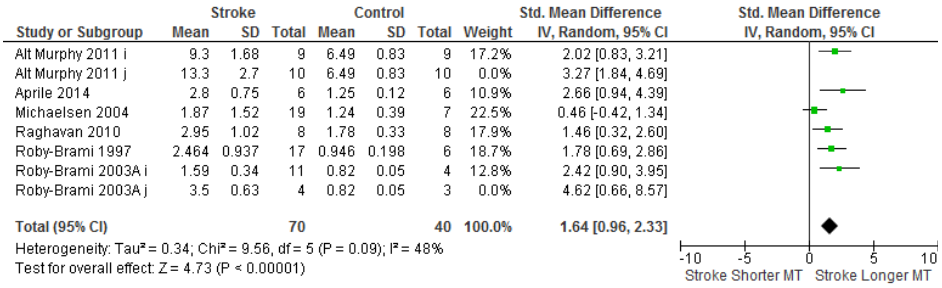


Figure 9B. SMD of MT in the central workspace excluding participants with moderate stro

Figure 9C

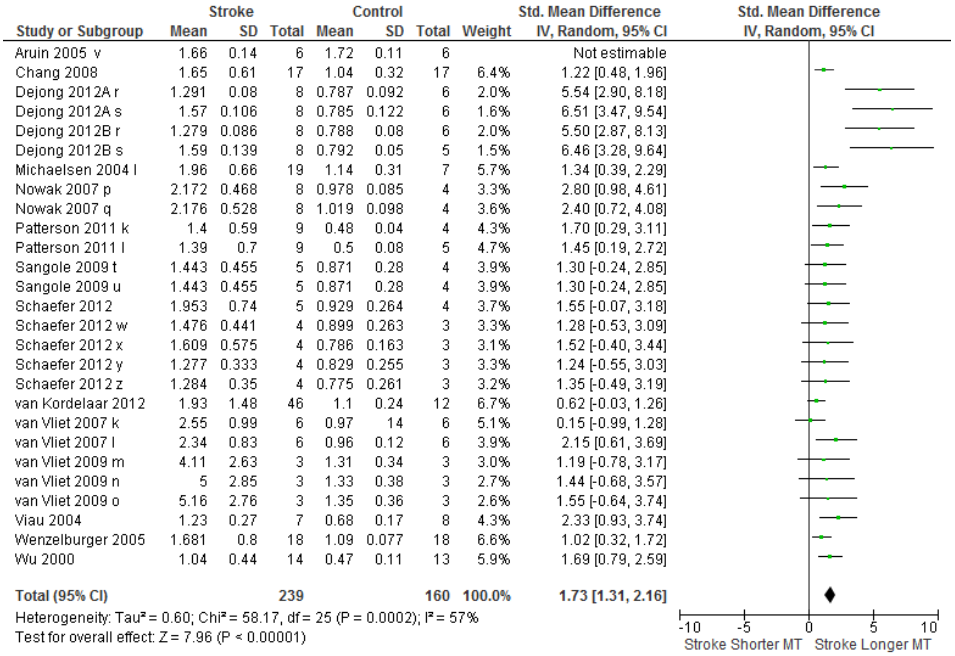


Figure 9C. SMD of MT in the ipsilateral workspace excluding participants < 3 months after stroke

Figure 9A, B, C - Sensitivity analyses (SMD) of movement time during reach-to-grasp comparing stroke survivors to neurologically intact controls based on upper limb motor impairment and time since stroke. A fixed effects model was used if $I^2 < 25\%$, a random effects model was used if $I^2 > 25\%$. The left side of the forest plot indicates a shorter movement time; the left side indicates longer movement time. Stroke survivors demonstrate significantly longer movement times in the central and ipsilateral workspace. MT=movement time, SMD=standardised mean difference

Figure 10 - Reach Path Ratio (object distance/path distance; 1 = straight path)

Figure 10A

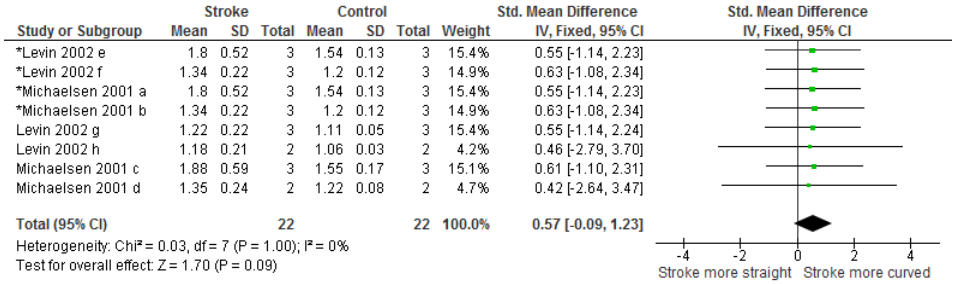


Figure 10A. SMD of RPR in the central workspace, all studies

Figure 10B

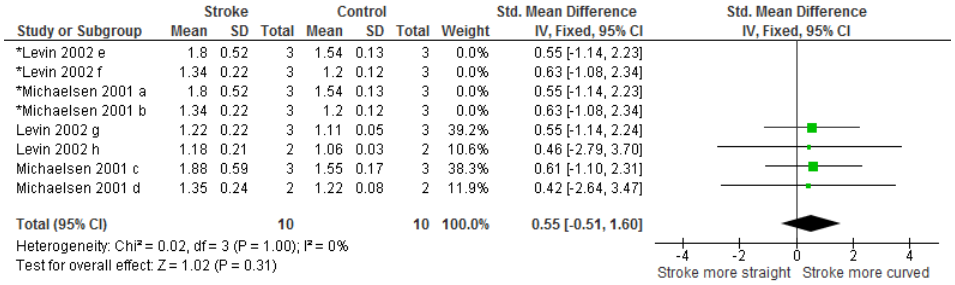


Figure 10B. SMD of RPR in the central workspace excluding potentially overlapping participants

Figure 10C

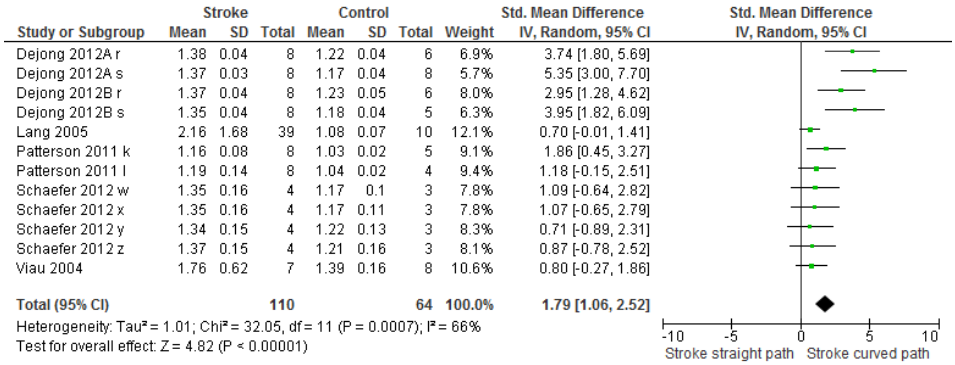


Figure 10C. SMD of RPR in the ipsilateral workspace

Figure 10A, B, C - Forest plots of the SMD of the reach path ratio comparing stroke survivors to neurologically intact participants reaching in the central and ipsilateral workspace. Studies with an * indicate potentially overlapping participants. A fixed effects model was used if $I^2 < 25\%$, a random effects model was used if $I^2 > 25\%$. The left of the forest plot indicates a straighter reach (exhibited by neurologically intact adults); the right side of the forest plot indicates a more curved reach path. Stroke survivors demonstrate a more curved reach path compared to neurologically intact control participants, with significant differences in the ipsilateral workspace. RPR=reach path ratio, SMD=standardised mean difference

Figure 11 - Sensitivity Analysis of Reach Path Ratio (object distance/path distance; 1 = straight path)

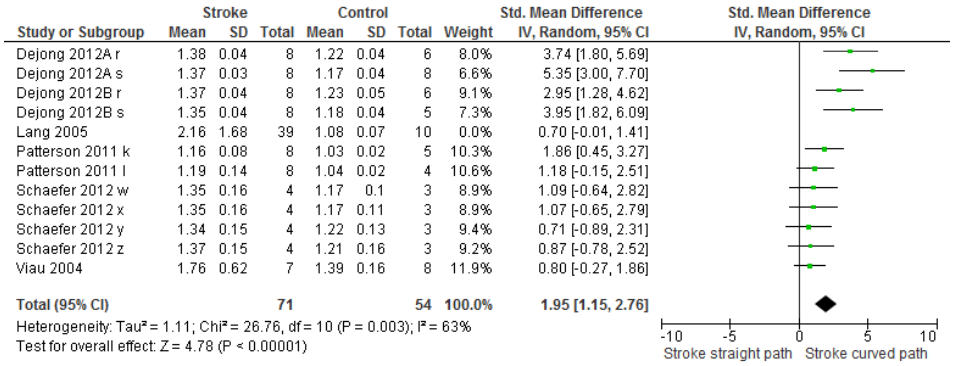


Figure 11 - Sensitivity analysis (SMD) of reach path ratio in the ipsilateral workspace comparing stroke survivors to neurologically intact control participants, excluding stroke survivors < 3 months after stroke. A fixed effects model was used if I^2 < 25%, a random effects model was used if I^2 > 25%. The left side of the forest plot indicates a straighter reach path to the object (similar to neurologically intact reaching), the right side indicates a more curved path. Stroke survivors demonstrate a significantly more curved reach path.

Figure 12 - Trunk Contribution during Reach-to-Grasp

Figure 12A

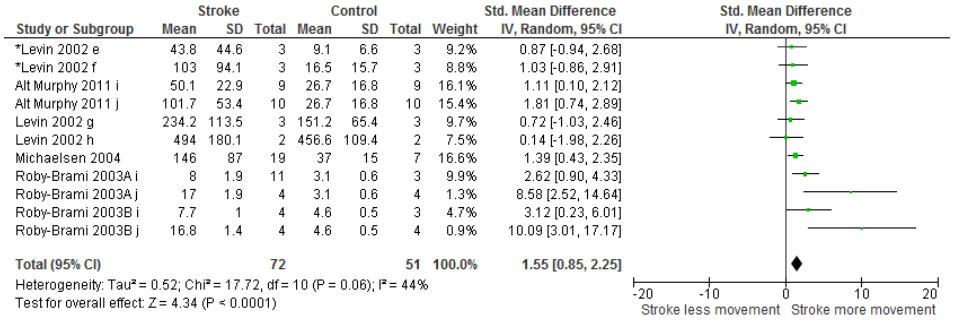


Figure 12 A. SMD of trunk contribution in the central workspace

Figure 12B

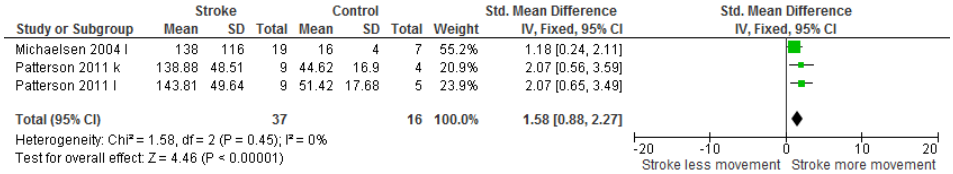


Figure 12B. SMD of trunk contribution in the ipsilateral workspace

Figure 12A, B. Forest plots of the SMD of trunk contribution during reach-to-grasp comparing stroke survivors to neurologically intact control participants in the central and ipsilateral workspace. A fixed effects model was used if $I^2 < 25\%$, a random effects model if $I^2 > 25\%$. The left side of the forest plot indicates less trunk movement during reach-to-grasp, the right side indicates more trunk movement during reach to grasp. Stroke survivors demonstrate significantly greater trunk displacement compared to neurologically intact control participants.

Figure 13 - Sensitivity Analysis Trunk Contribution during Reach-to-Grasp

Figure 13A

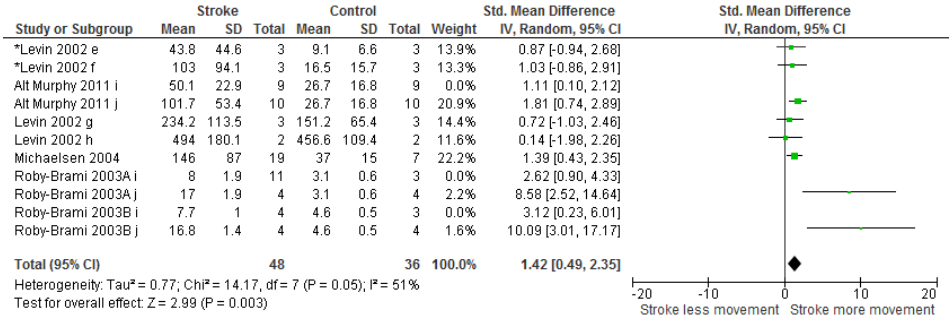


Figure 13A. Sensitivity analysis excluding stroke survivors with mild motor deficits

Figure 13B

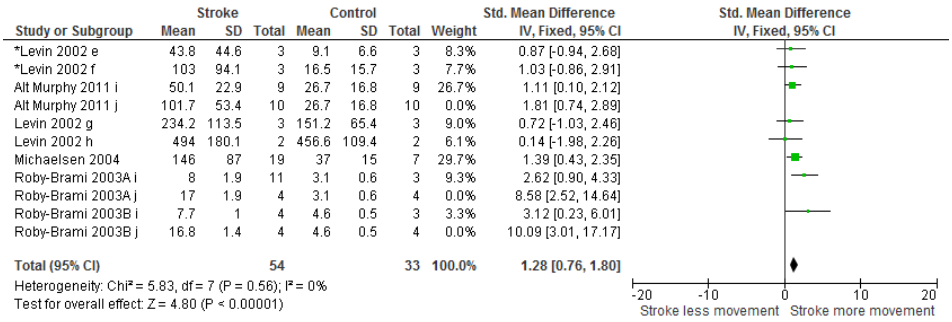


Figure 13B. Sensitivity analysis excluding stroke survivors with moderate motor deficits

Figure 13A, B. Sensitivity analysis (SMD) of trunk contribution during reach-to-grasp comparing stroke survivors to neurologically intact controls based on level of upper limb motor impairment. A fixed effects model was used if $I^2 < 25\%$, a random effects model was used if $I^2 > 25\ \%$. The left side of the forest plot indicates less trunk movement (displacement) during reach to grasp, the right side of the plot indicates greater trunk movement (displacement). Stroke survivors exhibit greater trunk displacement.

Figure 14 - Smoothness of Movement

Figure 14A

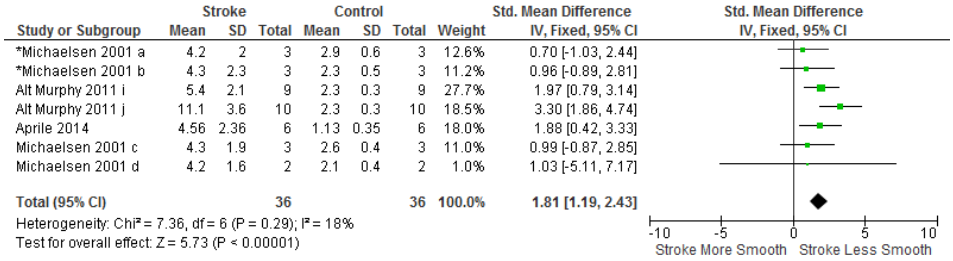


Figure 14A. SMD of movement smoothness in the central workspace

Figure 14B

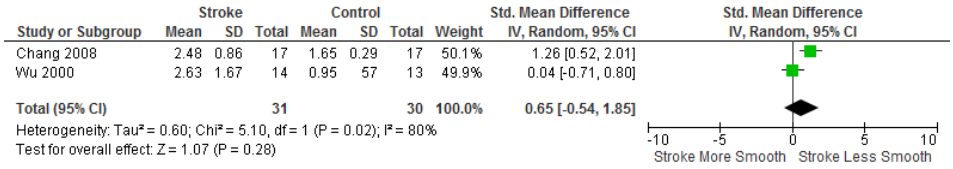


Figure 14B. SMD of movement smoothness in the ipsilateral workspace

Figure 14A, B - Forest plot of the SMD of movement smoothness during reach-to-grasp comparing stroke survivors to neurologically intact control participants in the central and ipsilateral workspace. A fixed effects model was used if $I^2 < 25$ %, a random effects model was used if $I^2 > 25\%$. The left side of the forest plot indicates smoother movement, the right side indicates less smooth movement (greater number movement units). Stroke survivors demonstrate significantly less smooth movement during reach-to-grasp in the central workspace.

Figure 15 - Sensitivity Analysis of Smoothness of Movement

Figure 15A

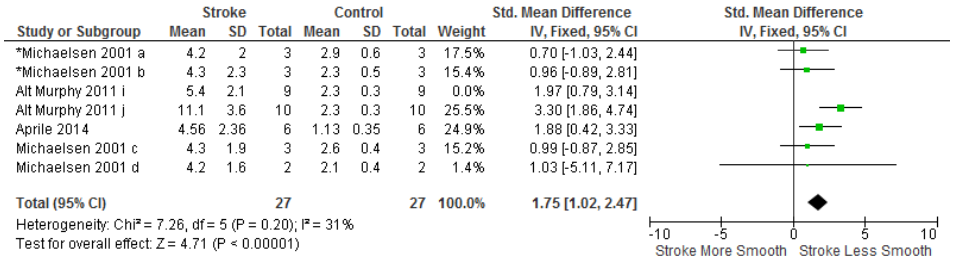


Figure 15A. Sensitivity analysis central workspace excluding participants with mild stroke

Figure 15B

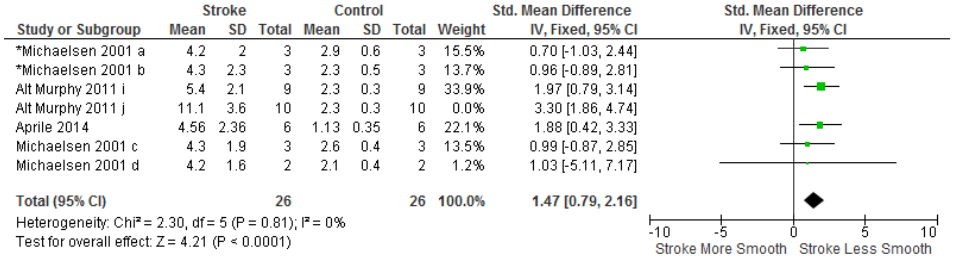


Figure 15B. Sensitivity analysis, central workspace excluding participants with moderate st

Figure 15A, B - Sensitivity analysis of smoothness of movement during reach-to-grasp comparing stroke survivors and neurologically intact control participants, based on level of upper limb motor impairment. A fixed effects model was used if $I^2 < 25$ %, a random effects model was used if $I^2 > 25\%$. The left side of the forest plot indicates smoother movement, the right side indicates less smooth movement (greater movement units). Stroke survivors demonstrate less smooth movement during reach-to-grasp when both stroke survivors with mild and moderate motor deficits are removed from the analyses.

Figure 16 - Forest Plots of Elbow Extension Range of Motion

Figure 16A

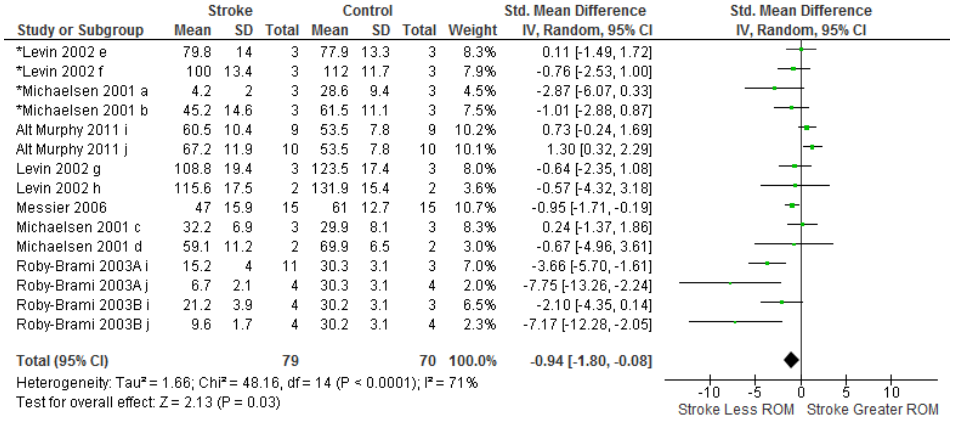


Figure 16A. SMD of elbow ROM in the central workspace, all studies

Figure 16B

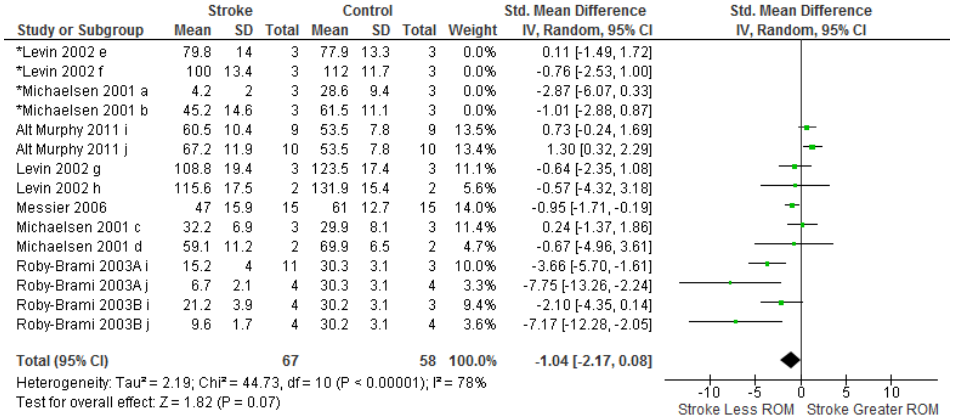


Figure 16B. SMD of elbow ROM in the central workspace excluding potentially overlapping participants

Figure 16A, B - Forest Plots of the SMD of elbow range of motion during reach-to-grasp comparing stroke survivors and neurologically intact control participants. A fixed effect model was used if $I^2 < 25\%$, a random effects model was used if $I^2 > 25\%$. The left side of the forest plot indicates a smaller range of motion, the right side of the plot indicates greater range of motion. Studies with an * indicate potentially overlapping participants. Stroke survivors demonstrate significantly less elbow range of motion than neurologically intact adults when reaching in the central workspace.

Figure 17 - Sensitivity Analysis Elbow Extension Range of Motion

Figure 17A

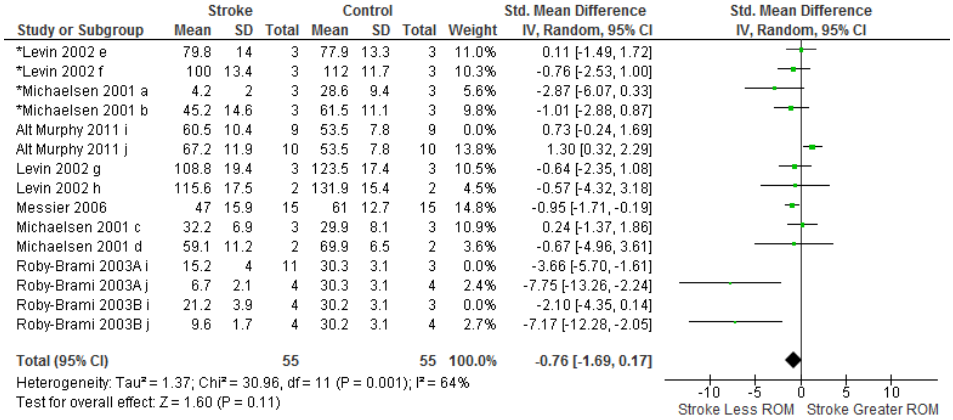


Figure 17A. Sensitivity analysis in the central workspace excluding participants with mild stroke

Figure 17B

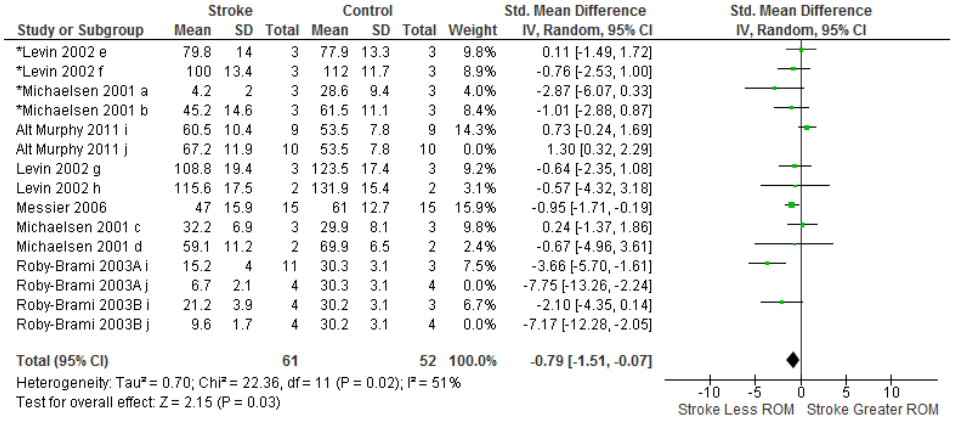


Figure 17B. Sensitivity analysis excluding participants with moderate motor deficits

Figure 17A, B - Sensitivity analysis of elbow range of motion during reach-to-grasp in the central workspace comparing stroke survivors to neurologically intact controls. The left side of the forest plot indicates smaller elbow range of motion, the right side indicates greater elbow range of motion. A fixed effect model was used if $I^2 < 25\%$, a random effects model was used if $I^2 > 25\%$. Studies with an * indicate potentially overlapping participants. Stroke survivors demonstrate less elbow extension than neurologically intact control when stroke survivors with both mild and moderate motor deficits are removed from the analysis.

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Key to Forest Plots

a. Trunk free target 1 (1/2 arm's length)
b. Trunk free target 2 (arm's length)
c. Trunk restrained target 1 (1/2 arm's length)
d. Trunk restrained target 2 (arm's length)
e. T1 1/2 arm's length
f. T2 arm's length
g. 1 1/3 arm's length
h. 2x arm's length
i. Good motor function
j. Poor motor function
k. Small object
l. Large object
m. Distance of 8 cm
n. Distance of 13 cm
o. Distance of 18 cm
p. Control R hand, stroke L hemisphere
q. Control L hand, stroke R hemisphere
r. Unilateral palmar grasp
s. Unilateral 3-finger grasp
t. Spherical
u. Cylindrical
v. Dominant arm of control group
w. 3-finger grasp hold
x. 3-finger grasp lift
y. Palmar grasp hold
z. Palmar grasp lift

3.4 Discussion and interpretation

The findings of the meta-analysis demonstrate that stroke survivors exhibit significantly lower peak velocity, longer movement time, decreased smoothness (exception ipsilateral workspace), increased curvature of reach path ratio (exception central workspace), greater trunk displacement, and less elbow extension compared to neurologically intact control participants during reach-to-grasp tasks. However, the primary studies included in the meta-analysis exhibited unclear or high potential risk of bias therefore the findings of the meta-analysis may also contain bias and should be interpreted with caution.

The findings of the meta-analysis are in line with earlier narrative reviews (Alt Murphy and Häger, 2015, McCrea et al., 2002, van Vliet et al., 2013), and extend these findings by providing statistical evidence of the differences in kinematics between stroke survivors and neurologically intact adults. Additionally, the meta-analyses have demonstrated that the kinematic differences between stroke survivors and neurologically intact adults are consistent when reaching in the central workspace or ipsilateral workspace (exception reach path ratio and movement smoothness). The search did not identify any studies that investigated reach-to-grasp in the contralateral workspace; reaching across midline into the contralateral workspace is commonly part of upper limb rehabilitation. It remains unknown how the kinematics during reach-to-grasp in the contralateral workspace may differ from the central or ipsilateral. This review has highlighted the heterogeneity of reach-to-grasp research and the need for standardisation of tasks and methods to ease comparison between studies

3.4.1 Potential risk of bias

The studies included in this review had unclear and high potential risk of bias. The observational study design utilized by a majority of the studies lends itself to more potential bias than randomized controlled trials. However observational design was an appropriate design choice for questions being addressed. Study designs would have been strengthened by the use of blinding. In rehabilitation research it is difficult to blind participants because they are actively participating in the intervention or in the case of this review the reach-to-grasp task. Probably of more importance for these studies is that there was insufficient attempt to blind the assessors. Although, kinematic and neurophysiologic outcomes are less susceptible to assessor bias compared to clinician administered standardised clinical measures such as the Wolf Motor Function Test. The potential for bias remains. This is because there is an interaction between assessor and the participants being assessed. For example, an assessor may give extra encouragement to a participant they get along with or connect with. The extra encouragement will decrease the standardization of the task and may influence the

results. The blinding of participants and of assessors is a key component of potential risk of bias assessments and a possible confounder.

Assessment of the potential risk of bias in systematic reviews of observational studies is a recent development. Mallen et al (2006) reported that systematic reviews of observational studies published between1999-2000, had only 22% of reviews assessing the quality (potential risk of bias) of included studies, compared to 50% of systematic reviews published in between 2003-2004. There exists a lack of potential risk of bias tools designed specifically for observational studies, and lack of consensus of which current tools would best assess potential risk of bias of non-RCT study designs. The lack of tools and consensus of observational studies is problematic in the assessment and interpretation of potential risk of bias, and in comparing potential risk of bias with other systematic reviews.

3.4.2 **Heterogeneity**

The studies included in this review were heterogeneous in nature such as variation in reaching task, upper limb motor ability, time since stroke, movement speed, trunk restraint, and methods of data collection and analysis. The heterogeneity can be both a positive and a negative. A possible negative of the heterogeneity is the complexity of combining the results of such varied tasks and participants within a meta-analysis (Higgins et al., 2008); the results of which may be biased. Alternatively, the heterogeneity may be positive. Firstly, despite heterogeneity the stroke participants' kinematics showed consistent patterns that were different to neurologically intact control participants' kinematics. Secondly, the variation may allow the findings of the meta-analysis to be generalizable to the wider stroke population. In future research the heterogeneity of reach-to-grasp research should be addressed. A consensus as to which reach-to-grasp tasks most replicate ADL's, which tasks are most sensitive to change, and the most appropriate methods of data collection and analysis is needed to develop a standardized assessment. The standardization of reach-to-grasp tasks and methods of data collection may lead to kinematic assessment becoming more commonplace in the clinical setting, not only in research.

3.4.3 **Limitations**

A limitation of this review is that it was limited to studies published in the English language contributing to a potential publication bias. The prerequisite ability to complete reach-to-grasp may potentially bias the findings towards stroke survivors with moderate to mild motor deficits. The search strategy was comprehensive; however it is possible that relevant studies were not identified.

A second limitation is the combination of heterogeneous studies within a meta-analysis (Higgins et al., 2008). The studies included in the review exhibited clinical diversity

(variability in participants) and methodological diversity (variability in reach-to-grasp task and methods of data collection and analysis (Higgins et al., 2008). Despite the heterogeneity the findings of the individuals studies were similar; previous systematic reviews have combined heterogeneous studies (Lohse et al., 2014, Cooke et al., 2010a). The I^2 statistic demonstrated 0% heterogeneity for five meta-analyses, less than 25% heterogeneity for one meta-analysis, between 25% and 70% heterogeneity for ten meta-analysis and only one meta-analysis demonstrated an I^2 value of > 70% exhibiting high heterogeneity (Higgins et al., 2008, Ried, 2006). Evaluation of the forest plots demonstrates that many of the confidence intervals overlap and the mean differences all fall on the same side of the line of no effect (Higgins et al., 2008) suggesting the findings of the studies are comparable.

3.4.4 **Clinical implications for physical therapy**

Implementing a treatment plan for the upper limb is complex. There are many facets that therapists must consider when planning a reach-to-grasp activity to create and maintain an appropriate level of complexity and challenge. For example, therapists need to determine what task (goal), body positioning, object placement, movement speed, trunk use or trunk restriction, and type of feedback. The kinematic differences between stroke survivors and neurologically intact adults are consistent during reach-to-grasp in the ipsilateral or central workspace. This finding will allow therapists to focus on other aspects of the reach-to-grasp task such as movement speed, object size, trunk restraint and type of feedback to increase or decrease challenge. There was substantial potential risk of bias and heterogeneity of included studies, thus definitive targets for interventions cannot be determined. Future investigations could evaluate if interventions targeted at the kinematic differences may improve the underlying movement deficits, improve reach-to-grasp, and increase independence with ADL's. Furthermore, of importance to stroke survivors as well as clinicians is the ability of a measurement to tool to be able to identify and measure a meaningful functional change in upper limb function.

It is useful to identify understand the kinematic differences in reach-to-grasp after stroke. Yet, the clinical and functional relevance of the differences is also important such as establishing the minimal clinically important difference (MCID). The MCID is the amount of change in a kinematic characteristic that is clinically important to stroke survivors (Portney and Watkins, 2009). The MCID of walking speed has been estimated in individuals 20-60 days after stroke that a change greater than 0.16 m/s of comfortable walking speed is clinically important (Tilson et al., 2010). There is a lack of research in the MCID of upper limb kinematic characteristics. Research has identified the minimal detectable change (MDC), the minimal amount of change that is not attributable to chance in upper limb kinematics. The findings revealed that reach path ratio, endpoint error, and inter-joint coordination demonstrated smaller MDC and thus may be better

suited to detect real change in upper limb movement (Wagner et al., 2008). Building on the present research future investigation of the MCID of kinematic characteristics is needed for upper limb therapy to have functional relevance for stroke survivors as well as improve assessment and interpretation of longitudinal change in kinematics.

3.3.1 Conclusion

In summary kinematic characteristics between stroke survivors and neurologically intact controls are consistently different during reach-to-grasp in central and ipsilateral workspace. Therefore, therapists can focus on the other aspects of the reach-to-grasp task to maintain challenge.

Future research should address standardisation of reach-to-grasp task and of data collection and analysis. Investigations combining the assessment of observational clinical measures, and kinematic assessment and assessment of the neural correlates of reach to grasp may provide comprehensive knowledge of the interaction between clinical impairments, kinematics, and neural control of movement.

4 Test-Retest Reliability of TMS Measures of Corticospinal Pathway Excitability Across the Lifespan

4.1 Introduction

Transcranial magnetic stimulation has been used with neurologically intact adults to develop knowledge of the connection between the motor cortex and the muscles of the arm and hand e.g. (Devanne et al., 2002, Levin et al., 2011, Ridding and Rothwell, 1997, Pearce et al., 2000), to investigate neural plasticity e.g.(Pearce et al., 2000, Pascual-Leone et al., 1995, Perez et al., 2004), and to induce virtual lesions to probe the contribution of specific brain areas to movement (Vollmer et al., 2015, Narayana et al., 2014). TMS studies in neurologically intact adults have been mainly focused on young adults, typically younger than forty years old (Boroojerdi et al., 2001, Civardi et al., 2001, Kamen, 2004, Carroll et al., 2001) with a lack of research in older adults. Although the research is useful, there is a possible limitation to the concentration in younger adults, such as using their data as normative data to compare to stroke survivors in which the incidence increases with age (Xanthakis et al., 2014). The aging process is associated with changes within the body's systems, specifically the nervous system and is associated with decreases in motor control.

Normal aging is accompanied by a decrease in white matter within the brain, decreases inter-hemispheric connections via the corpus collusum and decreased density and number of myelinated neurons within the corticospinal pathway (Seidler et al., 2010, Salat et al., 2005). The changes within the nervous system and aging are associated with older adults, demonstrating different areas of brain and corticospinal activation compared to younger adults completing the same motor task. For example, older adults recruit additional brain areas (McGregor et al., 2011, Sailer et al., 2000, Talelli et al., 2008b), additional neurons, (Kossev et al., 2002), demonstrate earlier activation of the corticospinal pathway (in preparation for movement) (Levin et al., 2011), and decreased inter-hemispheric inhibition (Marneweck et al., 2011, Talelli et al., 2008b), compared to younger adults. Older adults also exhibit decreased motor control; such as decreased coordination/dexterity (Marneweck et al., 2011, Sullivan et al., 2010), decreased reaction time (Levin et al., 2011), and decreased strength (Plow et al., 2014).

The recruitment of additional brain areas as well as neurons and earlier activation of the corticospinal pathway in older adults is hypothesized to be a means of compensation to maintain a specific level of motor control or coordination to complete the task. The age-related changes within the CNS and suggest that TMS findings within young adults may not be applicable to older adults; this is evident in TMS measurement of the elements of the MEP.

The measurement of MEP elements yields different findings in older adults compared to younger adults, however the evidence is inconsistent. For example, previous research has exhibited the MEP amplitude in older adults to be smaller (McGinley et al., 2010, Oliviero et al., 2006); larger (Kossev et al., 2001); and no different to younger adults (Stevens-Lapsley et al., 2012). Despite the inconsistent findings, there is evidence of changes within the corticospinal pathway and its measurement with aging. The changes within TMS measurement of the MEP further support that TMS measurement in young adults may not be applicable to older adults. TMS measurement in neurologically intact adults is used to develop normative data for comparison to individuals with neurological disease such as stroke. The current normative TMS data has been investigated with young adults. However, individuals with neurological disease such as stroke tend to be older adults (Xanthakis et al., 2014). TMS measurement in older adults is lacking and necessary for age-matched comparison with stroke survivors. If inferences about the nervous system are going to be drawn from TMS measurement it is important that the measurement be stable.

An important aspect of measurement is the reliability of a measure or measurement tool within the population that it is being used or investigated. The test-retest reliability of TMS measures has been investigated in young healthy adults demonstrating moderate to good reliability e.g. (Carroll et al., 2001, Malcolm et al., 2006, Ngomo et al., 2012). The reliability findings from individual studies are in Table 4 in Chapter 0 page 51. Age related changes in the brain and corticospinal pathway, and the changes in the MEP elements, may influence the test-retest reliability of TMS measures. There is a lack of TMS reliability research in older adults. Two studies have investigated the test-retest reliability of TMS measures in older adults (Christie et al., 2007, Schambra et al., 2015). However, these studies were limited to assessment of hand muscles such as adductor digiti minimi (Christie et al., 2007) and first dorsal interosseous (Schambra et al., 2015), as well as limited to assessment of MEP amplitude (Christie et al., 2007), motor threshold, and the recruitment curve (Schambra et al., 2015). It is known that not all muscles respond equally to TMS, for example the distal proximal gradient (Martin et al., 2006). It is expected that the reliability of TMS measurement will be different for different muscles. It is therefore essential to expand investigations beyond the hand muscles to the muscles of the forearm and upper arm muscles as all the muscles of the upper limb work together to have functional use of the arm and hand (Shumway-Cook and Woollacott, 2007). It remains unknown how the aging nervous system may influence the test-retest reliability of other MEP elements and other upper limb muscles, which are necessary for ADL's.

In addition to age there are other factors that may contribute to variability in TMS measurement. There is evidence that caffeine, physical activity, cortisol (time of day) and

nicotine can influence corticospinal excitability and magnetic stimulation. However this evidence in inconsistent. Caffeine has been found in some research to increase MEP amplitude (Specterman et al., 2005) and lengthen the silent period (Cerqueira et al., 2006), yet other research found caffeine had no influence on these elements (Orth et al., 2005). Physical activity was found to be beneficial for brain-muscle connectivity; physically active older adults exhibited silent periods that were more similar to younger adults compared to sedentary older adults (McGregor et al., 2011). Cortisol is a hormone associated with circadian rhythms (sleep/awake cycles), when levels are low such as in the afternoon and evening neural plasticity is enhanced and the MEP response is more reliable (Sale et al., 2008, Sale et al., 2007). Finally, nicotine has also been associated with neural plasticity. When nicotine was withdrawn in a group of smokers neural plasticity was decreased (Grundey et al., 2012). It would be a challenge to attempt to control for all of these factors in research. If all of the above factors were controlled for the sample, it may not be representative of the general population or individuals with neurological disease.

The aim of this study is to answer research question 2a “Is TMS measurement of corticospinal pathway excitability reliable (test-retest reliability) in neurologically intact adults of all ages (> 18 years of age)”? This study will determine the test-retest reliability of TMS measures of corticospinal pathway excitability, investigating: the motor threshold, MEP amplitude, MEP latency, silent period, and recruitment curve of the bilateral biceps, extensor carpi radialis, and abductor pollicis brevis. A secondary aim of this study is to answer research question 2b “Is the reliability of TMS measurement influenced by age, gender, physical activity or dexterity?” This study will determine if age, dexterity, and other factors such as physical activity influence the test-retest reliability of TMS measures of corticospinal pathway excitability (listed above).

4.2 Methods

4.2.1 Ethical approval and informed consent

Ethical approval was provided by the UEA Faculty of Medicine and Health Ethics Committee. Ethical approval was granted on 6 February 2014, reference 2013/2014-20. Associated approval letters are in Appendix 3 and 4. An amendment was approved on 20 June 2014 to include pregnancy on the medical screening questionnaire as an exclusion criteria to participating in TMS. All data was stored on a password protected computer that only the researcher and her supervisors had access to.

All participants provided written informed consent prior to taking part in the project (Appendix 5). Participants were given at least 24 hours to read the information sheet before agreeing to take part in the study. Any questions participants had regarding TMS or the procedures were answered via email, telephone conversation, or in person. Upon arrival to the first session the procedures were reviewed with participants and any questions answered. Written informed consent was obtained after participants questions were answered satisfactorily. A copy of the signed informed consent form was given to each participant. Upon arrival to the second session, the procedures were again reviewed and any questions answered. Participants were asked if they wished to continue with the second session, if they answered “yes” the second session of TMS was conducted.

4.2.2 Research design

This study uses a prospective correlational test-retest reliability study design. The test-retest reliability of TMS measures of corticospinal pathway were assessed over two identical TMS sessions. The two TMS sessions were identical and separated by 5-7 days (Julkunen et al., 2009, Liu and Au-Yeung, 2014).

4.2.3 Participants

Participants were recruited from the local community via posters (Appendix 6). The posters were placed around the UEA campus and sent electronically in the staff and school bulletin emails. In addition, the poster was displayed in public spaces such as the (city) library and also in the public areas of charities such as Age UK. The researcher spoke about the research project at Age UK, the Norfolk Older People’s Forum, and the Positive about Aging conference. Interested participants contacted the researcher via email or phone call. Interested participants were then emailed a summary of the research project and the participant information sheet detailing the purpose and procedures of the research project (Appendix 7). TMS suitability questions were included in the participant information sheet in the form of a health screening questionnaire (Appendix 8). The health screening questions were based on the contraindications to TMS such as implanted metal, pacemaker, drug infusion pump,

hydrocephalus shunt, epilepsy, and pregnancy (Rossi et al., 2009). An answer of 'yes' to any of the health screening questions meant participants were not suitable to participate in TMS. Participants that met the inclusion criteria and wanted to take part after reading the participant information sheet, had TMS arranged at a convenient time for them. All questions were answered prior to obtaining informed consent.

The participants in the TMS reliability study of neurologically intact adults were not age matched to those in the reliability study of stroke survivors early after stroke (Chapter 5). Both studies were run as pragmatic studies. Age-matching was not feasible as the studies were running in parallel and recruitment of stroke survivors was dependent on the FAST INdICATE trial. Additionally, the methods were slightly different for the neurologically intact adults maintaining a specific percentage of their MVC during data collection compared to the stroke survivors maintaining a slight contraction monitored by the researcher.

4.2.4 **Power Calculation**

The power calculation is based on the estimation of the ICC to within a pre-specified level of confidence via the estimation of a confidence interval (Portney and Watkins, 2009, de Vet et al., 2006). As the lower limit for "acceptable reliability" is 0.7 this was set to be the lower bound of the confidence interval, the other parameter required is the estimated value of the ICC. Previous literature has estimated the ICC to be between 0.6 and 0.94 (Mylius et al., 2013, Bastani and Jaberzadeh, 2012, Cacchio et al., 2009), it was decided to use 0.8 as this is within the limits of previous research and represents an acceptable level of reliability. This means that the confidence interval should have a width of 0.2 (from 0.7 to 0.9) and using standard formulae this gives the required number as 51 per group.

Table 15 - Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. At least 18 years of age	1. Younger than 18 years of age
2. No known neurological disorder	2. Known neurological disorder
3. Ability to participate in TMS assessed by completion of the health screening questionnaire (Appendix 8)	3. Not suitable to participate in TMS assessed via health screening questionnaire (Appendix 8)

Table 15 - Inclusion and exclusion criteria to determine suitability to participate in the study.

4.2.5 **Equipment**

The following sections describe the equipment used during a TMS session.

4.2.5.1 **TMS Equipment**

Single pulse TMS was delivered using a Magstim 200^2 (Magstim Company Ltd, Carmarthenshire, UK) stimulator with a figure of 8 coil (90 mm in diameter), see Figure 18A and B. The EMG/MEP data was collected using surface EMG electrodes. ConMed Cleartrace ECG surface electrodes (ConMed Patient Care, Utica NY, USA) 20 mm in diameter (Figure 18C), were used to collect data from the biceps brachii (BB) and extensor carpi radialis (ECR) muscles.

Nicolette cup electrodes (Figure 18D) with conducting gel/electrode cream (Grass EC2 electrode cream, Grass Products Natus Neurology Middleton WI, USA) were used to collect data from the abductor pollicis brevis (APB).

The EMG signals were pre-amplified filtered and sampled using a Digitimer Ltd. Pre-amplifier (Digitimer Ltd, Hertfordshire, UK), as seen in Figure 18E, the CED (Cambridge Electronic Design) Micro 1401 (Cambridge Electronic Design Limited, Cambridge UK), and the Neurolog System (Digitimer Ltd, Hertfordshire, UK) both displayed in Figure 18F.

Figure 18 - Equipment used during TMS Session

Figure 18A. Magstim 200[2] Stimulator

Figure 18B. Figure-of-8 TMS coil

Figure 18C. ConMed Cleartrace electrodes used to collected muscle activity from the BB and ECR

Figure 18D. Cup Electrodes used to collect muscle activity from the APB

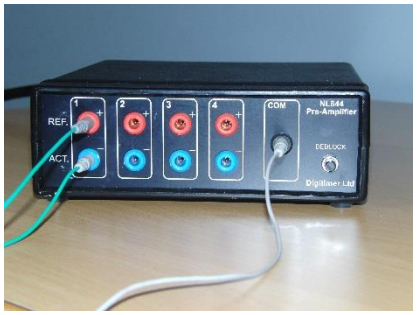


Figure 18E. Digitimer Ltd Pre-amplifier

Figure 18F. Neurolog (top shelf) and Cambridge ElectronicDesign (CED) Micro 1401 (bottom shelf)

Figure 18 - Equipment used during a TMS session A: TMS machine, B: figure-of-8 coil, C: surface EMG electrodes, D: cup electrodes, E: Digitimer, Neurolog, and F: Cambridge Electronic design (CED) Micro 1401. TMS=transcranial magnetic stimulation

4.2.5.2 **Myometer**

Participants' maximal voluntary contraction (MVC) was assessed using the MTE Medical Research limited myomometer displayed in Figure 19. The myomometer was also used during active TMS conditions to provide a visual cue target for participants to maintain 20% of their individual MVC (Talelli et al., 2008b, Rothkegel et al., 2010, Liu and Au-Yeung, 2014, Cacchio et al., 2009).

Figure 19 - MTE Myometer

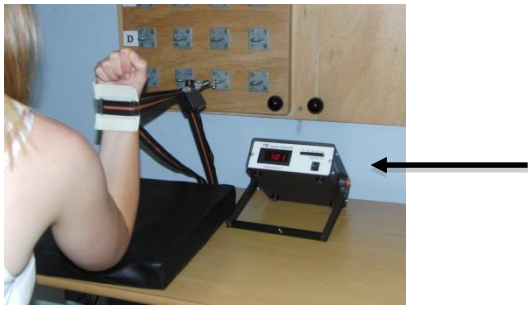


Figure 19 - MTE myometer being used to assess the strength of a biceps contraction.

4.2.6 **Muscles of investigation**

The muscles of investigation were the biceps brachii, extensor carpi radialis, and abductor pollicis brevis of both the dominant and non-dominant upper limbs. These muscles were selected because they are essential for completion of activities of daily living such as dressing and grooming. The biceps assists in transport of the arm in space and flexing the elbow. The extensor carpi radialis stabilizes and extends the wrist enabling finger dexterity. The abductor pollicis brevis abducts the thumb to allow for grasp and object manipulation (Nowak, 2008, Shumway-Cook and Woollacott, 2007). The distal upper limb muscles such as the ECR and APB, have been frequently studied in previous research, (Corneal et al., 2005, Massie and Malcolm, 2013, Malcolm et al., 2006, Sollmann et al., 2013, Wassermann, 2002); whereas the biceps are less frequently studied (Harris-Love et al., 2015) but essential to reach to grasp and functional use of the upper limb. There is evidence that the upper limb muscles respond differently to TMS (Martin et al., 2006) and the reliability of TMS measures is different in different muscles. The reliability of the motor map of the EDC (ICC=0.86) and FCR (ICC=0.85) were higher than for the APB (ICC=0.68) and FDI (ICC=0.63) (Malcolm et al., 2006); the reliability of the recruitment curve also demonstrated higher ICC values for the FDI (ICC=0.85) compared to the FCR (ICC0.36-0.76) (Carson et al., 2013).

The dominant limb has been most frequently studied in previous research (Malcolm et al., 2006, Sollmann et al., 2013, Wassermann, 2002); however a number of recent studies have investigated both dominant and non-dominant upper limbs (Koski et al., 2005, Kimiskidis et al., 2004) and non-dominant limbs (Ngomo et al., 2012). Individuals use both their dominant and non-dominant limbs throughout the day to complete activities of daily living. Research by Koski et. al. (2005) found that when using TMS, the coefficient of variation of both the motor threshold and silent period were different in the dominant compared to the non-dominant hemispheres/limbs. Corticospinal projections may be different to the dominant and non-dominant limb.

4.2.7 **Procedures**

Procedures for session 1 and session 2 were identical and detailed in Figure 20.

Figure 20 - Procedures during TMS Session

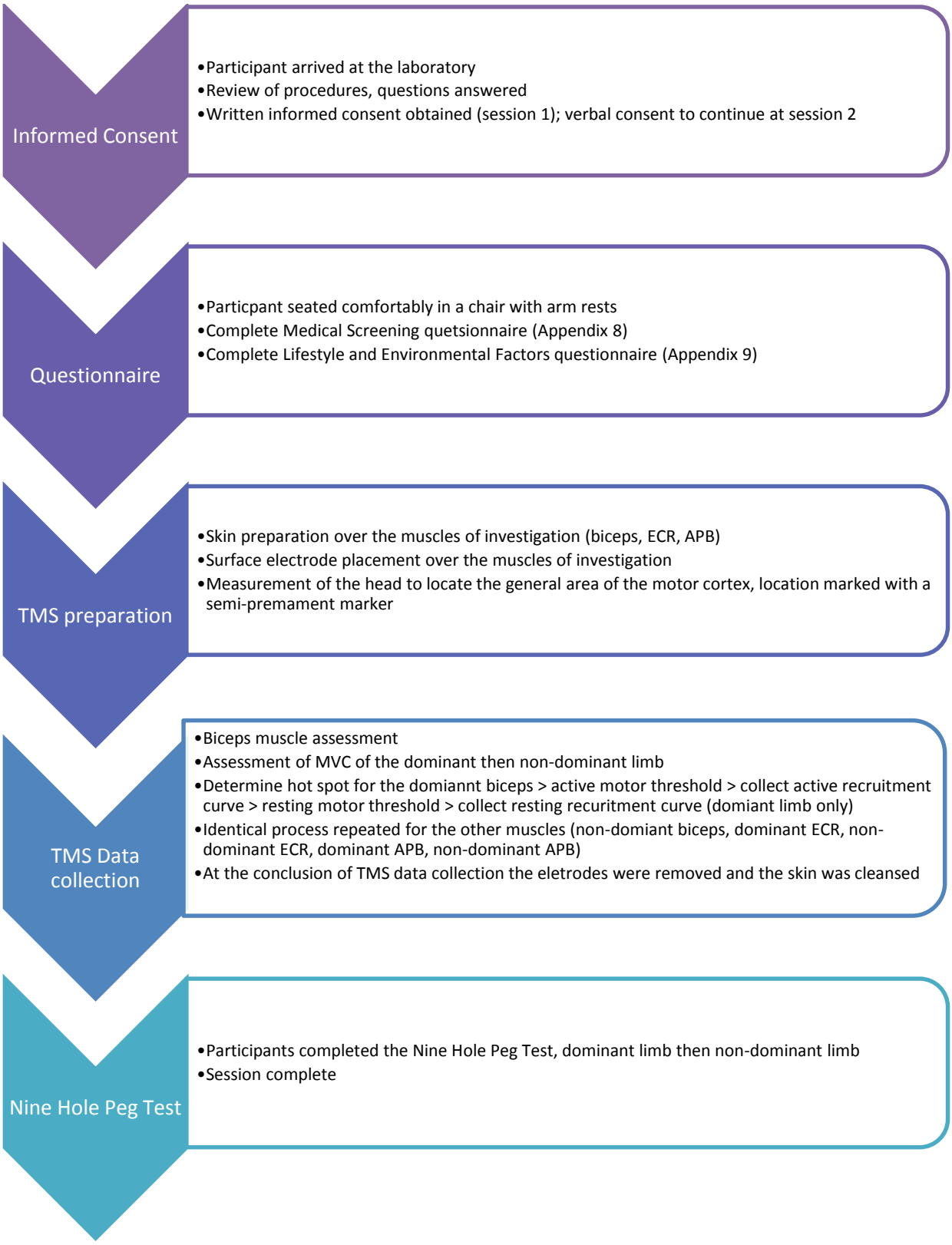


Figure 20 Details the procedures during the TMS sessions.

4.2.7.1 **Health screening and lifestyle factors questionnaire**

Participants were seated comfortably in a chair with arm rests for the duration of the TMS session. Participants completed a health screening questionnaire (Appendix 8) to determine their suitability to participate in TMS described in section 4.1.3 page 115. Once suitability to participate in TMS was determined participants then completed a lifestyle and environmental factors questionnaire (Appendix 9). This questionnaire included questions relating to age, handedness, exercise participation, medications, occupation, caffeine intake, and smoking; all of which have been found to influence the corticospinal pathway and neural plasticity. Assistance was given as needed to complete the questionnaires.

4.2.7.2 **Electrode placement**

Next, the skin over the muscles of investigation were cleansed with NuPrep gel (Weaver and Company, Aurora, Colorado 80011) and an alcohol swab. Participants were requested to gently contract their muscle to identify the muscle belly. Electrodes were placed in parallel along the muscle fibres of the biceps, extensor carpi radialis, and abductor pollicis brevis of both the dominant and non-dominant limbs (Ngomo et al., 2012); Figure 21. A ground electrode was placed on the olecranon process. The electrodes were connected to the pre-amplifier with leads.

Figure 21 - Surface EMG Electrode Placement

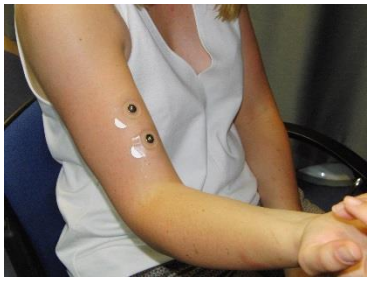


Figure 21A. EMG electrode placement on the biceps muscle.

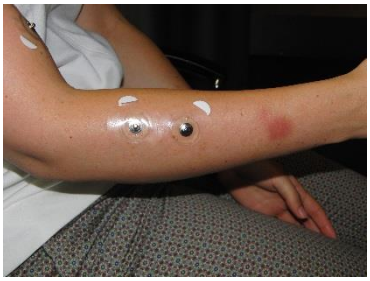


Figure 21B. EMG electrode placement on the extensor carpi radialis muscle.

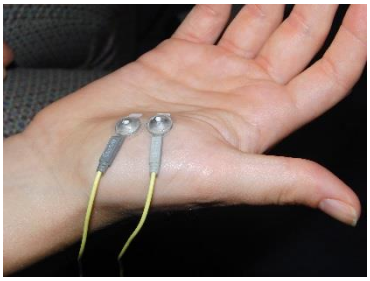


Figure 21C. EMG electrode placement on the abductor pollicis brevis .muscle

Figure 21 - Placement of the surface electrodes for the biceps, ECR, and APB during TMS. ECR=extensor carpi radialis, APB=abductor pollicis brevis, TMS=transcranial magnetic stimulation

4.2.7.3 **Location of the motor cortex**

To determine the general location of the motor cortex the participant's head was measured using a soft tape measure Figure 22. The head was measured anterior to posterior, the median distance marked on the scalp with a marker. The head was then measured from ear to ear, the median distance again marked on the scalp with a marker. From the middle of both marks a distance of six centimetres laterally and two centimetres anteriorly is measured and marked on the scalp with a marker. This is the general area of the motor cortex which corresponds with the upper limb muscles.

Figure 22 - Measurement of the Head for Locating the Motor Cortex

Figure 22A. Measure the head anterior (between the eyebrows) to posterior (base of skull). The median distance was marked on the scalp.

Figure 22B. Measure the head laterally from mid ear to mid ear. The median distance was marked on the scalp.

Figure 22C. Starting at the midpoint between the two measurements, another mark was placed on the scalp 6 cm laterally and 2 cm anteriorly.

Figure 22 - A, B, C Picture representation of the process of measuring the head to determine the general area of the motor cortex. This is the starting point to determining the hotspot of the muscles of the upper limb.

4.2.7.4 **Data collection**

TMS data collection was initiated once determination of the general area of the motor cortex was complete. The muscles were investigated in the following order: dominant biceps, non-dominant biceps, dominant extensor carpi radialis, non-dominant extensor carpi radialis, dominant abductor pollicis brevis, and non-dominant abductor pollicis brevis. The procedures of data collection were identical for each muscle and are described below Figure 23.

Figure 23 - Processes of TMS data collection

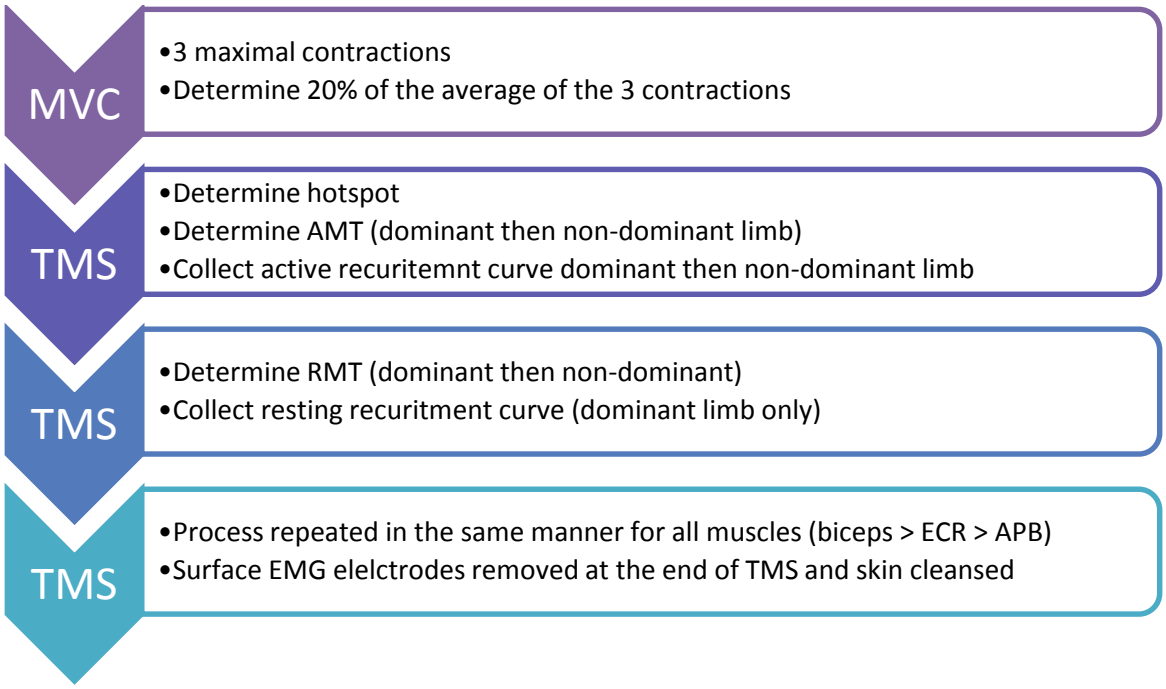


Figure 23 - Flow chart describing the processes of TMS during a session. Processes were identical at session 1 and session 2. The maximal voluntary contraction was assessed, 20% of the average MVC was maintained during active TMS conditions via visual feedback from the myometer. TMS data was then collecting starting with the AMT, active recruitment curve, RMT resting recruitment curve (dominant limb only), this process was repeated for all muscles.

- Maximal Voluntary Contraction
    - The researcher demonstrated each movement prior to the participant completing the movement.
    - Participants sat in front of a table; table height at mid-abdomen.
    - To assess the biceps maximal voluntary contraction (MVC), the participant placed their elbow on the table, with their elbow stabilised on the table, elbow flexed, and palm facing them.
    - The myometer strap was placed around the ventral surface of the forearm.
    - The participants were instructed to pull the strap towards them as hard as they could, generating a maximal biceps contraction (Figure 24 A).
    - The maximum value of Newtons was recorded. This process was repeated three times. The mean of the three trials was used as the MVC.

Figure 24 - Myometer Positioning

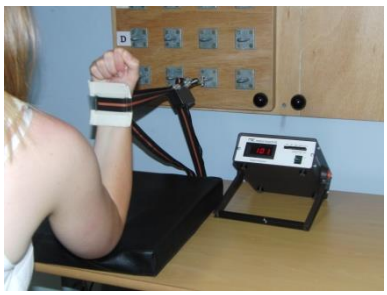


Figure 24A. Positioning for assessment of biceps strength and during TMS data collection.

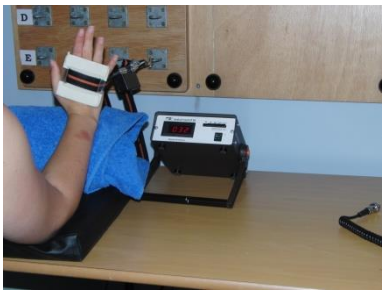


Figure 24B. Positioning for assessment of extensor carpi radialis strength and during TMS data collection.

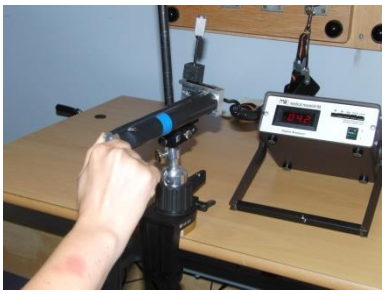


Figure 24C. Positioning for assessment of abductor pollicis brevis strength and during TMS data collection.

Figure 24 - Picture demonstration of maximal voluntary contraction (MVC) assessment of the biceps muscles (A), ECR (B), and APB (C). The same positions were maintained during active trials of TMS in which participants maintained 20% of their individual MVC.

- TMS
    - The EMG signals were pre-amplified at 10 Hz, 1 k gain, and filtered at 10-50 Hz. Motor evoked potentials were collected and saved for offline analysis using Signal 5.7 software.
    - The EMG data was collected in 500 ms samples, 100 ms prior to the TMS stimulus and 400 ms after the TMS stimulus.
    - The TMS coil was placed tangentially to the scalp over the area of the motor cortex contralateral to the muscle of interest with the handle

pointing backward to obtain a posterior-anterior current flow to the motor cortex, as illustrated in Figure 25 (Wassermann, 2002, Koski et al., 2005).

Figure 25 - Coil Position during TMS Data Collection

Figure 25 - Coil placement on scalp during TMS collection; tangential to the scalp to obtain a posterior to anterior current flow.

- Using the mark on the head as a guide (moving the coil when necessary to determine the hot spot) the hot spot for the dominant biceps muscles was determined. During muscle contraction the hot spot for the biceps was determined. The hot spot is the coil location on the scalp that the largest and most consistent MEP's are obtained from the muscle of interest (Carroll et al., 2001). Once the hot spot was determined the location was marked on the scalp with semi-permanent marker. All data related to the dominant biceps was collected from this scalp location.
- During active trials of TMS, participants arm was positioned on the table with the elbow supported and the myometer strap around the ventral surface of the forearm identical to the positioning during determination of the MVC. Participants were requested to maintain about 20% MVC (Talelli et al., 2008b, Rothkegel et al., 2010, Liu and Au-Yeung, 2014, Cacchio et al., 2009), using the Newtons on the myometer as visual feedback of their muscle contraction.
- The active motor threshold was determined while participants maintained a biceps contraction which was about 20% of their MVC. The stimulator output was initially placed at a suprathreshold level and was decreased in 5% increments, then when closer to the threshold stimulator output was decreased in 1-2% increments until half of the successive trials produced an MEP > 200 µv (Liu and Au-Yeung, 2014, Rossini and Rossi, 2007, Koski et al., 2007a).

- Once the active motor threshold was determined a recruitment curve was obtained (while participants maintained 20% MVC). Stimulation intensities in the recruitment curve were 100%, 110%, 120%, and 130% of active motor threshold; five TMS pulses were delivered at each intensity (Massie and Malcolm, 2013). Rest breaks were given as needed. Collecting data during active muscle contraction may decrease the potential for variability in excitability of the corticospinal pathway due to normal fluctuations (Koski et al., 2007a, Kiers et al., 1993). Often TMS studies investigating stroke survivors are conducted during active muscle contraction; thus having active muscle contraction data in neurologically intact adults is beneficial for comparison.
- Next, the resting motor threshold was determined in the same manner as the active motor threshold. The resting motor threshold was the threshold that half of consecutive trials had a MEP amplitude of > 50 μv (Ngomo et al., 2012, Rossini and Rossi, 2007). A resting recruitment curve was then collected at stimulation intensities of 90%, 100%, 110%, 120%, and 130% of resting motor threshold; five TMS pulses were delivered at each intensity. The resting recruitment was only collected on the dominant limb.
- This exact process was then repeated for the non-dominant limb and bilateral extensor carpi radialis and abductor pollicis brevis muscles.
- At completion of TMS the electrodes were removed and the skin was cleansed.
- All data was saved in Signal 5.7 software for offline analysis

- Nine Hole Peg Test (NHPT)
  - The NHPT is an assessment of hand dexterity. Published normative data can be found in a paper by Grice et al. 2003
  - The test involves taking pegs individually from a container and placing them into holes on the pegboard as quickly as possible. Once all of the pegs are placed in the holes the pegs are immediately removed individually and placed back into the container as quickly as possible
  - Figure 26) (Grice et al., 2003).
  - The test is timed; starting from when the participant touches the first peg till the last peg is placed back in the container.
  - Instructions for the NHPT were explained and moving the pegs was demonstrated by the researcher.

- Each hand was tested separately starting with the dominant hand. One practice trial was given and then one test trial

Figure 26 - Nine Hole Peg Test

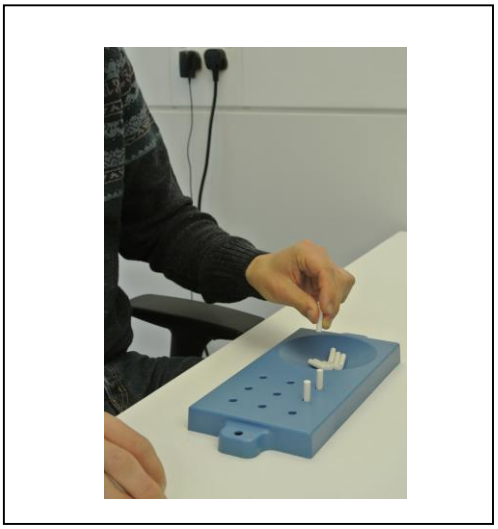


Figure 26 - Nine Hole Peg Test; placing of pegs from the well into the holes

- At completion of the NHPT the session was complete
- The second session was identical to the first session except that verbal consent to continue with the procedures was obtained

4.2.8 **Data processing**

The MEP elements investigated were active and resting motor threshold, recruitment curve slope, MEP latency, MEP amplitude, and the silent period. All MEP data was saved in Signal 5.7 software and analysed off-line. The researcher visually assessed each trial of TMS stimulation. Visual inspection involved determination if there was an MEP present, or if there was electrical noise that would inhibit analysis. Trials without an MEP or with electrical noise were not analysed. Frames that were appropriate for analysis were then tagged in the software.

4.2.8.1 **Motor threshold**

Determination of the motor threshold has been detailed in section 4.2.7.4 page 126. In summary the motor threshold was the stimulator output in which half the trials yielded an MEP of > 50 µv at rest and > 200 µv with a muscle contraction (Koski et al., 2005, Liu and Au-Yeung, 2014, Rossini and Rossi, 2007).

4.2.8.2 **MEP amplitude**

The MEP amplitude was the peak to peak amplitude or the maximum deflection-minimum deflection in μv of the MEP (Koski et al., 2007a). Frames to be analysed were tagged, and cursors placed on either side of the MEP Figure 27 - MEP amplitude. The maximum-minimum deflection between the two cursors was determined using a pre-written script in the Signal 5.4 software. The MEP max was the largest amplitude MEP within the recruitment curve.

Figure 27 - MEP amplitude

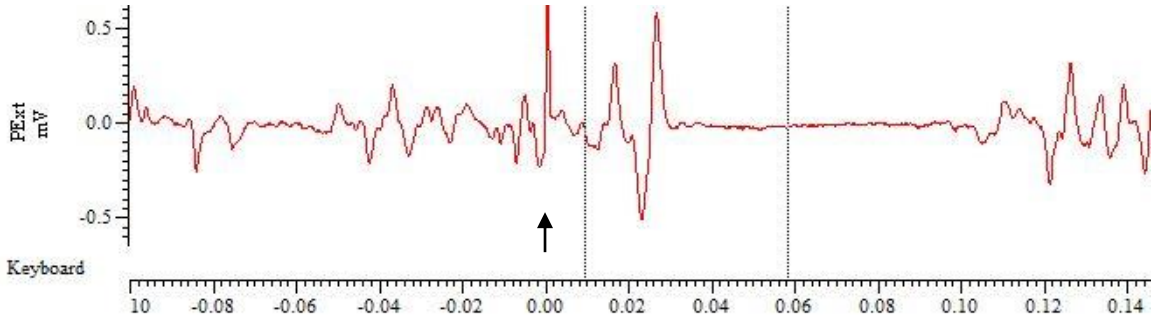


Figure 27 - Example of EMG following TMS stimulus; between the two grey vertical cursors is the MEP. The X axis is the time in ms, the y axis is the amplitude of EMG in mV, and the arrow is pointing to the TMS stimulus which occurs at 0.00 ms.

4.2.8.3 **MEP latency**

The MEP latency was determined by placing a cursor at the onset of the MEP. MEP onset was defined as the first sustained crossing of the rectified EMG trace prior to the first MEP peak Figure 28 (Rossini et al., 2010, Daniel et al., 2015, Koski et al., 2007b, Cacchio et al., 2009, Wassermann et al., 2008). Visual assessment of the first sustained crossing of the rectified EMG is common commonly used to determine the start of the MEP (Rossini et al., 2010, Daniel et al., 2015, Koski et al., 2007b, Cacchio et al., 2009, Wassermann et al., 2008). Alternatively, the start of the MEP can be determined using a mathematical approach such that the first crossing is three standard deviations above pre-stimulus EMG reflecting the start of the MEP (Cacchio et al., 2011). The time in milliseconds (ms) from TMS stimulus to the cursor is the MEP latency (MEP onset- TMS onset) (Koski et al., 2007a). A second researcher assessed 10% of participants for agreement in MEP latency, the researchers needed to be in agreement on at least 80% of trials. The two researchers' latencies were in agreement within 2 milliseconds of each other in 84% of the trials. Two milliseconds was selected based on previous research of the standard error of measurement and the minimal detectable change of MEP latency (Cacchio et al., 2011, Fisher et al., 2013). In instances in which the difference was greater than two seconds the two researchers met, investigated the data, and agreed

upon the value. Despite the variability in measurement of the MEP latencies, the latencies identified in this study were generally comparable to previous research (Julkunen et al., 2009, Furby et al., 1992, Eisen and Shtybel, 1990, Kossev et al., 2001).

Figure 28 - MEP Latency

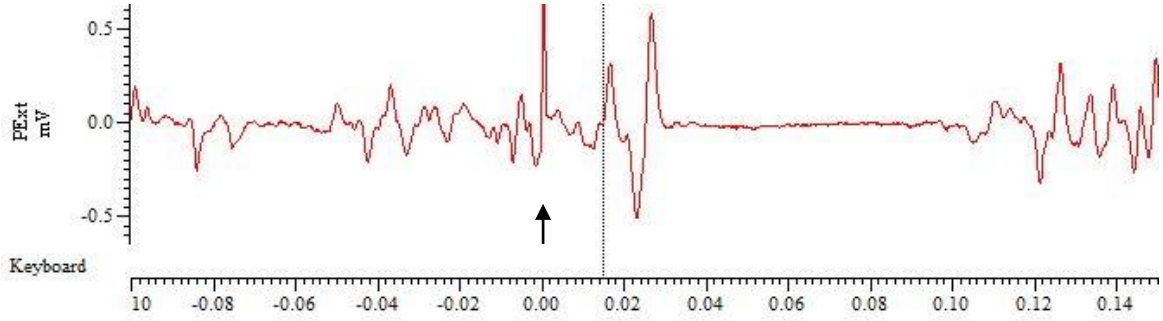


Figure 28- Example of EMG following TMS stimulus. The MEP latency is the time from TMS stimulation (arrow) 0.00 ms to the dotted grey cursor measured in ms (14.9 ms) The end of MEP latency is the start of the MEP. The x axis is the time in ms the y axis is the amplitude of EMG in mV. ms=milliseconds, EMG=electromyography, MEP=motor evoked potential

4.2.8.4 **Recruitment curve**

Recruitment Curve also known as the input-output curve, is a graph that depicts the increase in TMS stimulus against the increase in MEP size. The recruitment curve was plotted in Stata 12.1 using a sigmoidal function (Carroll et al., 2001, Carson et al., 2013, Liu and Au-Yeung, 2014). The elements of the recruitment curve that were analysed include the x intercept, slope, and area under the curve.

Figure 29- Recruitment Curve

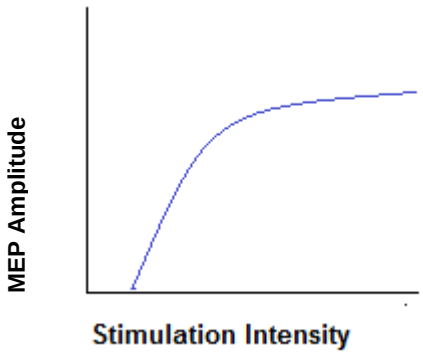


Figure 29 Example recruitment curve. The x-axis is the increasing stimulus intensity and the y-axis is the increasing MEP amplitude.

4.2.8.5 **Silent period**

The onset of the silent period was defined as MEP onset, the offset was return of EMG Figure 30 (Damron et al., 2008, Liu and Au-Yeung, 2014). The silent period was analysed via visual assessment (Damron et al., 2008). The silent period was assessed on all participants by one researcher, a second researcher independently assessed the silent period of 10% of participants. The two researchers were in agreement within 2 ms for 84% of trials.

Figure 30 - Silent Period

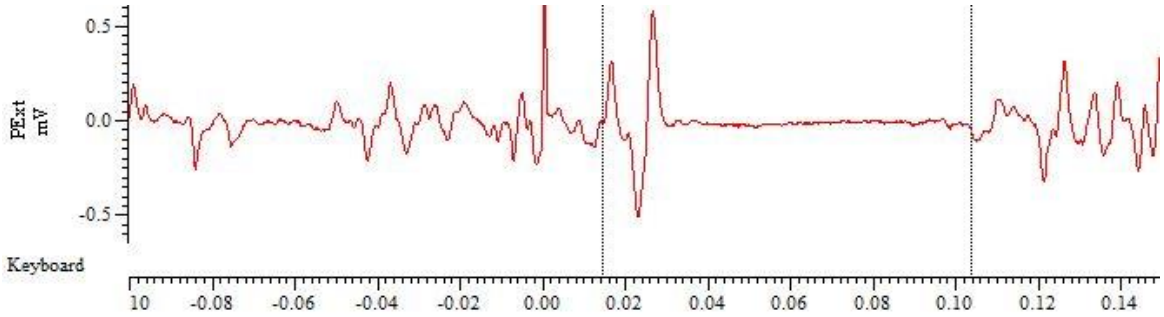


Figure 30 - Example of EMG after TMS stimulus. The silent period is the period is the duration between the two grey dotted cursors and measured in ms from onset of MEP (1st cursor) to return of EMG (2nd cursor). The x axis is the time in ms, the y axis is the amplitude of EMG in mV. mV=millivolts, MEP=motor evoked potential, ms=milliseconds TMS=transcranial magnetic stimulation

4.2.9 **Statistical analysis**

To answer research question 2a “Is TMS measurement of corticospinal pathway excitability reliable (test-retest reliability) in neurologically intact adults of all ages (> 18 years of age)?” the test-retest reliability was determined by the findings from session 1 to the findings of session 2.

The test-retest reliability was assessed using the Intraclass Correlation Coefficient (ICC), which reflects the degree of correlation as well as agreement between ratings; in other words how close the two scores are (Bruton et al., 2000, de Vet et al., 2006, Portney and Watkins, 2009). The ICC has the advantage that it supports generalizability in which the measured value is representative of the infinite distribution of possible values; thus the findings will be generalizable to the population (Portney and Watkins, 2009). The ICC has advantages over using a correlation coefficient such as Pearson’s product moment correlation (r). Pearson’s product moment correlation is limited in that it only measures the strength or degree of association between two variables, is unable to determine the agreement between the variables, and does not support generalizability.

As the total variance of the population studied gets larger the error component will account for a smaller proportion of the variance. For example, if the measurement error is small compared to the variability between individuals, the reliability parameter will be closer to one (de Vet et al., 2006, Portney and Watkins, 2009). However, the ICC is limited in that it cannot determine absolute agreement only the percentage of variance (Bruton et al., 2000, Portney and Watkins, 2009). Therefore, the Limits of Agreement (LOA) will also be used.

The LOA examines both agreement across multiple tests, as well as if there is a biased pattern of error such as systematic or random error (Bland and Altman, 1986b, Bruton et al., 2000, Portney and Watkins, 2009). Systematic error is predictable and occurs consistently in one direction; overestimating or underestimating the true score. Random error is error due to chance and is unpredictable (Bland and Altman, 1986b)

This study used the combination of the ICC and LOA to robustly determine the test-retest reliability of TMS measures. The ICC model [2,1] will be used to determine the test-retest reliability of the observations (de Vet et al., 2006, Portney and Watkins, 2009). The interpretation of ICC values was based on guidelines by Portney and Watkins (2009) (*Table 16*). Acceptable reliability for this study was an ICC of > 0.70; the lower end of the confidence interval used to determine acceptable reliability and the reliability category assigned within the results tables.

Other ways of investigating the reliability and agreement are through Cohen's kappa coefficient, Lin's Concordance Coefficient (CCC), standard error of measurement (SEM), coefficient of repeatability (CR). Cohen's Kappa is used to determine the agreement of categorical or ordinal data, and Lin's Concordance Coefficient determining the agreement between two different methods or raters (Portney and Watkins, 2009). In the present study the data were ratio and there was one assessor thus Cohen's kappa and CCC were not applicable. The SEM is related to response stability and measurement error; SEM is investigating how a repeated measure using the same instrument is distributed around the true score. A measure that has higher reliability will have smaller measurement error, and less variable distribution; thus the standard deviation of the measurement reflects the reliability of the response (SEM). A shortcoming of using SEM is that it is scale dependent, and there is a lack of guidance as to what value would be associated with acceptable reliability. Measurement error can be assessed from the Bland-Altman Plots and 95% Limits of Agreement which were used in this study (Portney and Watkins, 2009). The CR also referred to as the smallest real difference quantifies absolute reliability in measurement error and is directly related to LOA (Vaz et al., 2013). Identifying the smallest real difference is of value for TMS measurement. However, the step prior to determining the smallest real difference is determining if the measurement

tool provides reliable data that can be used to make clinical decisions. If the tool is not reliable then the smallest real difference may not need to be investigated. The present study was an exploratory study exploring the question is TMS reliable in neurologically intact adults of all ages. If TMS is found to be reliable the next steps would be to investigate the smallest real difference and minimal clinically important difference in future research; which would strengthen and refine the use of TMS to evaluate corticospinal pathway excitability and neural plasticity. The limits of agreement were used in the present study to investigate absolute reliability as well as provide a visual assessment of any potential bias in the difference in measurement between sessions (Bland and Altman, 1986a). Interpreting the ICC simultaneously with the LOA can provide both the correlation and agreement between sessions and the distribution of the differences.

Sub-group analysis will be completed for all MEP elements based on gender, age (≤ 49 years of age or ≥ 50 years of age), exercisers, and non-exercisers, dominant and non-dominant limbs. Individuals who exercise will be determined by self-report on the lifestyle and environmental factors questionnaire (Appendix 9). The study is not powered to statistically investigate differences in the reliability of the sub-groups of participants thus these analyses should be treated as exploratory. The sub-group analysis was conducted to better understand how the factors (exercise, hand dominance, age) may influence corticospinal pathway excitability and any potential trends in the reliability of TMS measures.

Statistical analysis was completed using STATA SE version 12.1 software.

Table 16 - Reliability Coefficient guidelines based on Portney and Watkins (2009)

Reliability Coefficient	Interpretation
< 0.50	Poor reliability
0.50 to 0.70	Moderate reliability
>0.70	Good reliability

Table 16 Guide to interpretation of the ICC

4.3 Results

4.3.1 Participants

Recruitment began in March 2014 and ended in June 2015. There were 54 individuals who showed interest in the study (Figure 31). One participant was prescribed psychotropic drugs that are known to influence brain stimulation studies and the MEP elements (Ziemann, 2004), thus he was excluded. A second participant gave informed consent but did not like TMS, no data was collected and the participant withdrew consent. A third participant was unable to attend the second session due to family commitments and thus their data was not analysed. Data was analysed on 51 participants. The mean age and standard deviation of participants was 43.7±16.4 years; there were 21 men and 30 women, further participant description is in Table 17, and the medications participants were taking in Table 18.

4.3.2 Adverse events

There were no adverse events as a result of TMS.

4.3.3 Nine Hole Peg Test

All participants completed the NHPT within the normal range associated with their age category (Grice et al., 2003).

4.3.4 Trials not included

There were 8% of trials were not included in the analysis due to an MEP not being present, or there was electrical noise inhibiting the analysis of the MEP.

Figure 31 - Flowchart of Recruitment

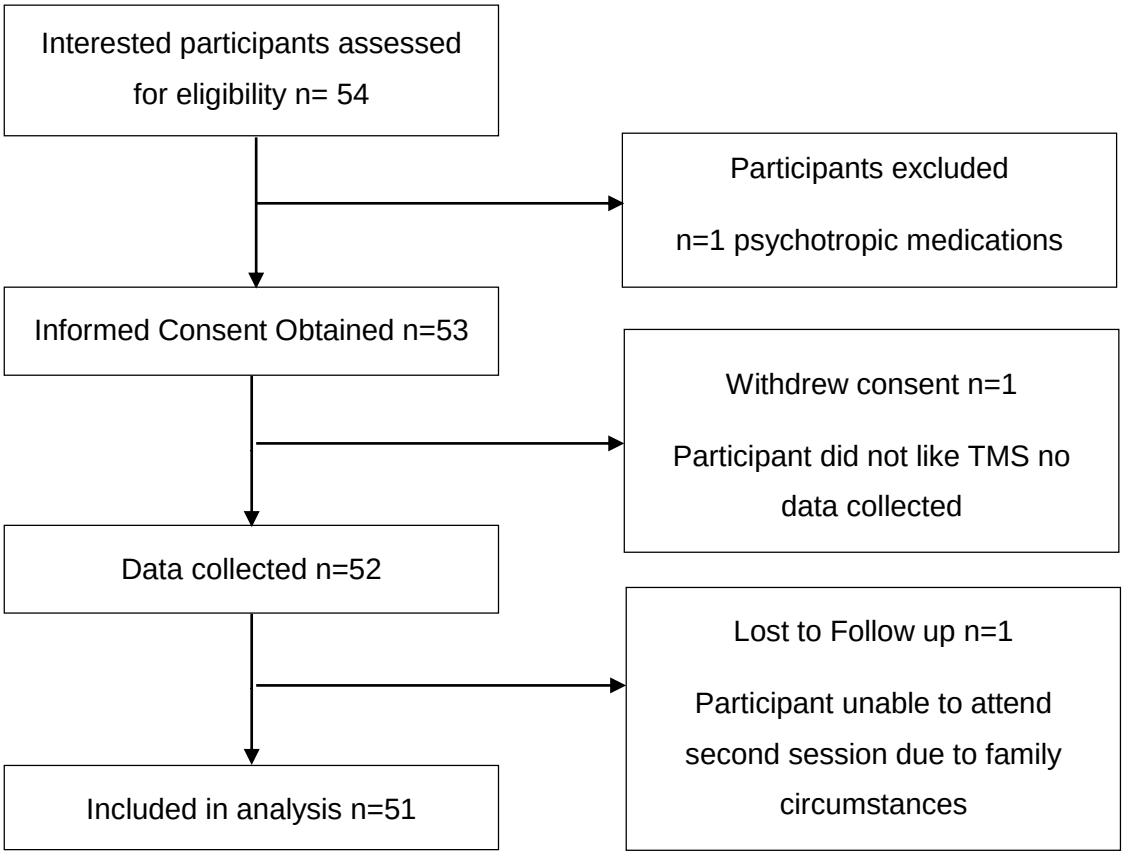


Figure 31 - Flow chart describing recruitment to the study. Fifty-four participants exhibited interest in the study, however one participant was on psychotropic medication which is known to influence brain stimulation thus was excluded. A second participant did not like TMS and withdrew consent and a third participant was unable to attend the second session and was therefore loss to follow up. Fifty-one participants were included in analysis.

Table 17 - Demographic & Lifestyle Questionnaire Responses and Nine Hole Peg Test Results

Questionnaire Question	**Response**
Participant age (mean and SD)	43.7±16.4 years (range: 21-74)
Gender	Male n=21 Female n= 30
Handedness	Right n=47 Left n= 4
Consume Caffeine	n=44
Participates in Exercise ≤ 3x a week > 3x a week	n=40 n=25 n=15
Medication (see Table 18 for medication list and uses)	n=20
Smoking	n=1
Nine Hole Peg Test	**Time To Complete**
Session 1	Dominant hand: 20.63±2.34 seconds Non-Dominant hand: 21.35±2.37 seconds

Table 17 - Participant responses to the lifestyle and environmental factors questions such as age, gender, handedness, consumption of caffeine, participation in exercise, and if they take medications.

Table 18 - Medications and Purpose

Medication	Number of Participants	Purpose
Amias	n=1	Candesartan, Anti-hypertensive
Novo-Serum RT	n=1	Collagen serum used externally on the skin
Thyroxine	n=1	Thyroid hormone supplement
Contraceptive Pill	n=4	Estrogen and progesterone used to prevent pregnancy
Nasal Steroid Spray	n=1	Corticosteroid nasal spray
Beclomethasone Inhaler	n=1	Asthma inhaler, corticosteroid
Fluoxetine	n=1	Serotonin reuptake inhibitor (SSRI) antidepressant
Bendroflumethiazide	n=1	Thiazide diuretic; anti-hypertensive and diuretic to reduce fluid
Lisinopril	n=1	ACE (angiotensin converting enzyme) inhibitor; anti-hypertensive
Metformin	n=1	Glucophage, antidiabetic treatment for type II diabetes (lowers blood sugar)
Simvastatin	n=1	Lipid (cholesterol) lowering medication
Terbinafine	n=1	Treatment of fungi, cream used externally on the skin
Venlafaxine	n=1	SSRI antidepressant
Lansoprazole	n=1	Proton pump inhibitor inhibiting stomachs production of gastric acid, treatment of ulcers
Chondroitin	n=2	Polysaccharide, treatment of osteoarthritis
Glucosamine	n=1	Amino sugar, treatment of osteoarthritis
Ventolin inhaler	n=2	Albuterol, bronchodilator, prevents bronchospasm in asthma
Ramipril	n=1	ACE inhibitor, anti-hypertensive
Ferritin	n=1	Intracellular protein that stores iron, treatment of anemia

Table 18 Describes the medications taken by participants included in the study and the number of participants taking the medication.

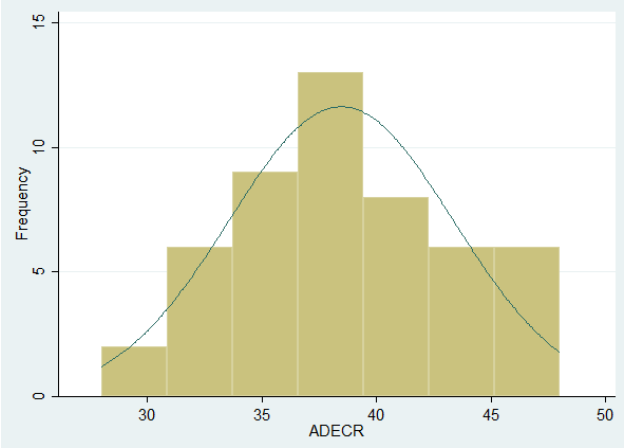
4.3.5 **MEP Elements**

The descriptive statistics (mean and standard deviation) of the MEP elements at session one and session two are in Table 19 for the motor threshold, MEP latency, silent period and the recruitment curve, Table 20 for the MEP amplitude 100% AMT to 130% AMT, and Table 21 for the MEP max amplitude. The data were roughly normally distributed. Example histograms for the motor threshold of the dominant and non-dominant ECR, and the MEP amplitude of the ECR assessed at 120% AMT are in

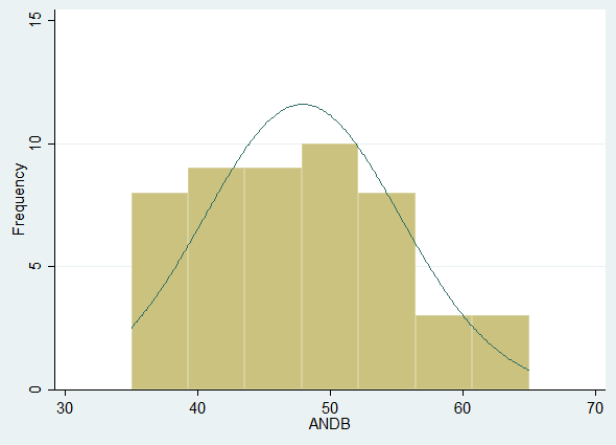
Figure 32 A to C respectively.

Figure 32 Histograms of Data Distribution

A. Active motor threshold dominant ECR



B. Active Motor Threshold Non-dominant Biceps



C. MEP amplitude of the non-dominant ECR at 120% AMT

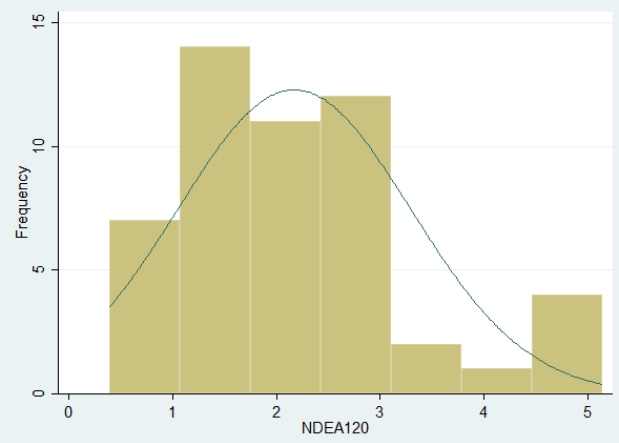


Figure 32 Histograms of data distribution demonstrating roughly normal distribution for the active motor threshold of the non-dominant biceps (A), dominant ECR (B) and MEP amplitude of the ECR at 120% AMT (C).

Table 19 Descriptive Statistics for MEP elements

Muscle	Dominant vs non-dominant	Testing Conditions	Motor Threshold Session 1	Motor Threshold Session 2	MEP Latency Session 1	MEP Latency Session 2	Silent Period Session 1	Silent Period Session 2	RC Slope Session 1	RC Slope Session 2
Biceps	Dominant	Resting	62 ±8.47	62 ±7.06	13.61±2.75	12.98±2.44			0.10±0.52	0.30±0.53
		Active	48 ±7.26	47 ±7.10	12.48±1.01	12.65±0.98	103.47±25.04	110.74±22.85	0.12±0.11	0.10±0.08
	Non-Dominant	Resting	62 ±6.84	63 ±6.60						
		Active	48 ±7.32	47 ±7.06	12.39±1.30	12.56±1.16	105.27±25.61	109.13±27.36	0.23±0.26	0.11±0.05
ECR	Dominant	Resting	48 ±6.87	49 ±8.01	17.90±1.51	17.65±2.16			0.13±0.070	0.42±0.50
		Active	38 ±4.86	38 ±5.03	16.48±1.52	16.40±1.48	98.03±28.21	100.61±28.66	0.21±0.38	0.09±0.07
	Non-Dominant	Resting	50 ±6.83	50 ±6.90						
		Active	40 ±4.92	40 ±5.27	16.38±1.57	16.08±1.21	107.45±35.43	106.33±37.27	0.14±0.07	0.12±0.063
APB	Dominant	Resting	49 ±7.07	49 ±7.31	23.65±2.76	23.24±2.38			0.20±0.15	0.16±0.12
		Active	41 ±5.24	40 ±4.55	22.93±1.87	22.59±1.72	126.56±31.05	137.48±33.05	0.17±0.12	0.19±0.20
	Non-Dominant	Resting	51±6.77	50 ±6.19						
		Active	42 ±4.95	41 ±4.43	22.31±2.22	22.49±2.30	133.29±40.03	131.79±39.25	0.17±0.16	0.14±0.12

Table 19 Describes the mean and standard deviation for the motor threshold, MEP latency, silent period, and slope of the RC at session one and session two for the biceps, ECR and APB. ECR=extensor carpi radialis, APB=abductor pollicis brevis, MEP=motor evoked potential, RC=recruitment curve

Table 20 Descriptive Statistics of the average MEP amplitude

Muscle	Dominant or Non-Dominant	% AMT	Average MEP Amplitude Session 1	Average MEP Amplitude Session 2
Biceps	Dominant	100	0.98 ±0.66	1.07 ±0.78
		110	1.22 ±0.77	1.54 ±0.75
		120	1.60 ±1.00	2.00 ±1.04
		130	1.97 ±1.13	2.37 ±1.30
	Non-Dominant	100	1.21 ±1.09	1.07 ±0.68
		110	1.66 ±1.37	1.54 ±0.94
		120	2.15 ±1.49	1.89 ±1.31
		130	2.62 ±1.98	2.20 ±1.43
ECR	Dominant	100	2.12 ±1.96	1.98 ±1.78
		110	2.55 ±2.11	2.42 ±2.03
		120	2.87 ±2.24	2.80 ±2.00
		130	3.05 ±2.21	3.30 ±1.97
	Non-Dominant	100	1.42 ±0.78	1.56 ±0.98
		110	1.84 ±1.04	1.91 ±1.09
		120	2.17 ±1.12	2.12 ±1.11
		130	2.38 ±1.14	2.34 ±1.23
APB	Dominant	100	1.43 ±1.28	1.06 ±0.55
		110	1.89 ±1.60	1.76 ±1.17
		120	2.54 ±1.86	2.53 ±1.58
		130	2.92 ±1.83	3.12 ±1.85
APB	Non-Dominant	100	1.97 ±1.88	1.61 ±1.51
		110	2.82 ±2.43	2.15 ±1.76
		120	3.54 ±2.58	2.81 ±2.16
		130	3.92 ±2.71	3.46 ±2.31

Table 20 Describes the mean and standard deviation of the average MEP amplitude at 100%AMT to 130% AMT for the biceps, ECR and APB. ECR=extensor carpi radailis, APB=abductor pollicis brevis, MEP=motor evoked potential, AMT=active motor threshold.

Table 21 Descriptive statistics of the MEP max amplitude

Muscle	Limb Assessed	Testing Conditions	MEP Max Amplitude Session 1	MEP Max Amplitude Session 2
Biceps	Dominant	Resting	1.68 ±1.36	1.26 ±0.96
		Active	2.55 ±1.51	2.92 ±1.64
	Non-Dominant	Resting		
		Active	3.21 ±2.17	2.71 ±1.73
ECR	Dominant	Resting	1.74 ±1.35	1.82 ±1.21
		Active	3.89 ±2.52	3.96 ±2.67
	Non-Dominant	Resting		
		Active	3.07 ±1.36	3.05 ±1.44
APB	Dominant	Resting	3.18 ±1.95	3.12 ±1.92
		Active	3.85 ±2.13	4.09 ±2.11
	Non-Dominant	Resting		
		Active	4.99 ±2.95	4.51 ±2.46

Table 21 Describes the mean and standard deviation of the MEP max amplitude for the biceps, ECR and APB during session one and session 2. ECR=extensor carpi radialis, APB=abductor pollicis brevis, MEP= motor evoked potential

4.3.6 **Reliability of MEP elements**

The reliability of the MEP elements investigated is variable within and among MEP elements. Each MEP element will be discussed individually.

4.3.6.1 **Motor threshold**

The test-retest reliability of the motor threshold for each individual muscle can be found in Table 22 to Table 24; the Bland-Altman Plots are in Figure 33 to Figure 38. Two participants found the higher stimulation intensities uncomfortable thus the motor threshold for the biceps was determined on 49 participants.

The motor threshold of the biceps muscle for all participants ranges from an ICC= 0.776 (0.639, 0.865) for the AMT of the non-dominant biceps to an ICC=0.676 (0.489, 0.804) for the RMT of the dominant biceps ICC= 0.676 (0.489, 0.804). The lower end of the 95% confidence interval falls within the moderate to poor range. The 95% CI and 95% LOA are wide indicating variability and imprecision in the measurement. The narrowest LOA are for the motor threshold of the non-dominant limb. The AMT tended to demonstrate higher ICC values than the RMT.

The Bland-Altman plots for the biceps demonstrate random error in agreement between measurements. The line of mean difference falls close to zero (no change between tests) for the group as a whole.

Table 22 - Test-retest reliability ICC and LOA of the motor threshold for the biceps muscle

Muscle	Participants	Active/Resting	Dominant/ Non-dominant	ICC (95% CI)	Reliability Category	95% Limits of Agreement
Biceps	Whole Group n=49	Resting	Dominant n=49	0.676, (0.489, 0.804)	Poor	-12.675 to 12.231
			Non-dominant n=46	0.756, (0.599, 0.858)	Moderate	-9.466 to 9.027
		Active	Dominant n=51	0.757, (0.612, 0.854)	Moderate	-9.303 to 10.895
			Non-dominant n=51	0.776, (0.639, 0.865)	Moderate	-9.089 to 10.477
Biceps	< 50 y/o n=31	Resting	Dominant	0.650 (0.394, 0.813)	Poor	-13.220 to 11.220
			Non-dominant	0.705 (0.480, 0.843)	Poor	-10.661 to 8.861
		Active	Dominant	0.797 (0.627, 0.895)	Moderate	-8.889 to 9.592
			Non-dominant	0.782 (0.603, 0.887)	Moderate	-8.503 to 9.476
Biceps	> 50 y/o n=18	Resting	Dominant	0.725, (0.390, 0.891)	Poor	-10.302 to 14.666
			Non-Dominant	0.868, (0.522, 0.960)	Moderate	-5.073 to 8.346
		Active	Dominant	0.651, (0.250, 0.857)	Poor	-10.275 to 14.608
			Non-dominant	0.771, (0.451, 0.911)	Poor	-10.946 to 13.613
Biceps	Women n=29	Resting	Dominant	0.666, (0.392, 0.831)	Poor	-13.351 to 12.791
			Non-dominant	0.735, (0.489, 0.872)	Poor	-10.572 to 9.663
		Active	Dominant	0.780, (0.577, 0.892)	Moderate	-10.008 to 13.222
			Non-dominant	0.722, (0.490, 0.859)	Poor	-8.859 to 12.145
Biceps	Men n=20	Resting	Dominant	0.655 (0.303, 0.848)	Poor	-12.120 to 11.820
			Non-dominant	0.784 (0.524, 0.911)	Moderate	-8.313 to 8.419
		Active	Dominant	0.730 (0.442, 0.881)	Poor	-7.638 to 7.067
			Non-dominant	0.862 (0.693, 0.942)	Moderate	-8.880 to 7.737

Muscle	Participants	Active/Resting	Dominant/ Non-dominant	ICC (95% CI)	Reliability Category	95% Limits of Agreement
Biceps	Non-exercisers n=11	Resting	Dominant n=11	0.570, (0, 0.864)	Poor	-10.770 to 10.952
			Non-dominant n=11	0.707, (0.223, 0.911)	Poor	-10.770 to 10.952
		Active	Dominant	0.778, (0.368, 0.935)	Poor	-13.390 to 14.556
			Non-Dominant	0.788, (0.381, 0.938)	Poor	-12.074 to 15.240
Biceps	Exercisers n=38	Resting	Dominant n=38	0.683, (0.469, 0.822)	Poor	-13.394 to 12.747
			Non-Dominant n=38	0.764, (0.580, 0.874)	Moderate	-9.295 to 8.134
		Active	Dominant	0.707, (0.509, 0.834)	Moderate	-7.868 to 9.597
			Non-Dominant	0.701, (0.504, 0.829)	Moderate	-7.914 to 8.725

Table 22 - The test-retest reliability of the motor threshold of the bilateral biceps brachii muscle of the whole group and subgroups based on age, gender, and participation in exercise. Reliability was assessed using the ICC and LOA. The ICC model used was [2,1] and the associated 95% CI, acceptable reliability is an ICC > 0.70. The 95% LOA were determined using Bland and Altman's 95% lower and upper limits of agreement; the difference between sessions was session 1 minus session 2, acceptable reliability is an ICC > 0.70. The lower end of the CI is in the range of poor reliability for most groups. ICC=intraclass correlation coefficient, LOA=limits of agreement, CI=confidence interval

Figure 33 - Bland-Altman Plots Resting Motor Threshold Biceps

A.

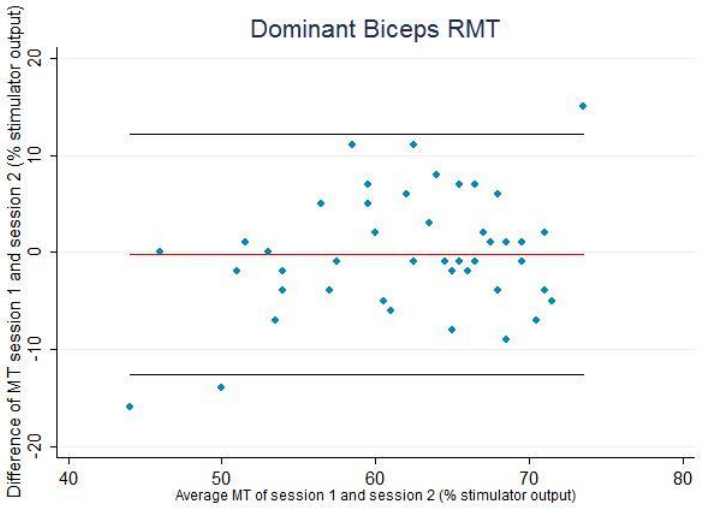


Figure 33 A. Bland-Altman plot of RMT of the dominant biceps n=49

B.

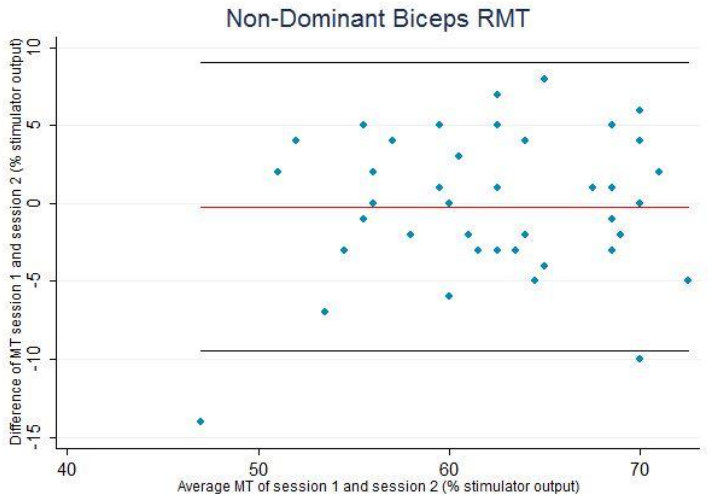


Figure 33 B. Bland-Altman plot of RMT of the non-dominant biceps n=46

Figure 33A & B - Bland-Altman plots of the RMT for the bilateral biceps muscle. The x axis is the average RMT of session 1 and 2 plotted against (y-axis) the difference in RMT between session 1 minus session 2, the red line indicates the mean difference between sessions. Plots A and B demonstrate random error in agreement between ratings. RMT=Resting motor threshold

Figure 34 - Bland-Altman Plots of Active Motor Threshold of the Biceps Muscle

A.

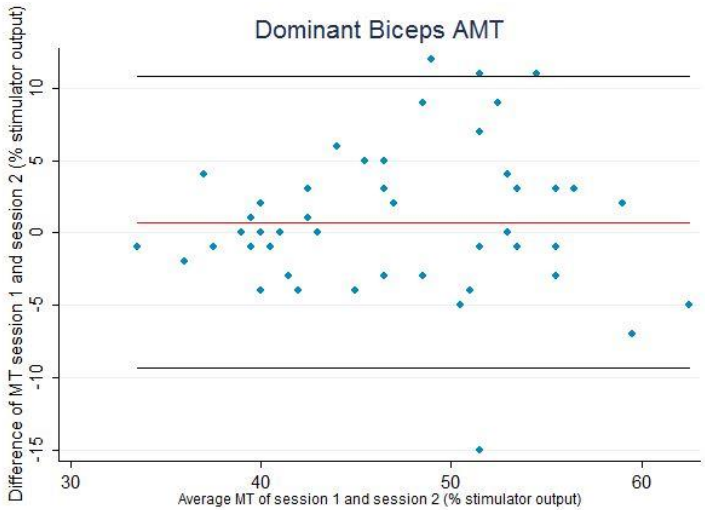


Figure 34 A. 95% LOA plot of AMT of the dominant biceps

n=51

B.

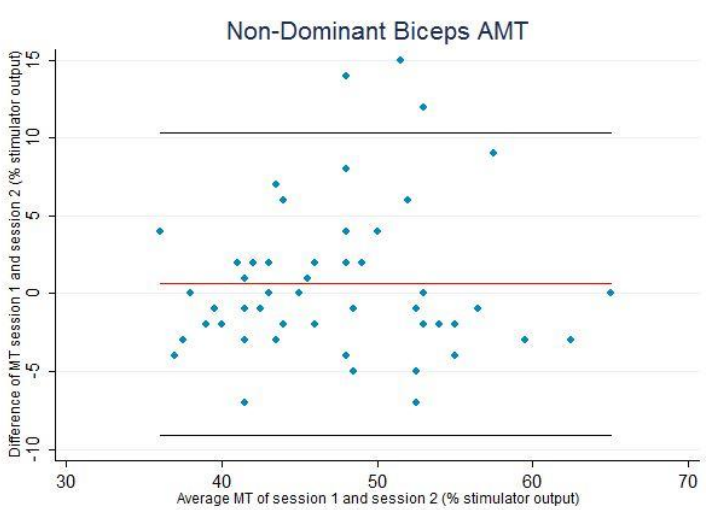


Figure 34 B. 95% LOA plot of the AMT non-dominant biceps

n=51

Figure 34 A & B - Bland-Altman plots of AMT of the bilateral biceps muscle assessed during 20% MVC background contraction. The x axis is the average AMT of session 1 and 2 plotted against the difference in AMT between session 1 minus session 2, the red line indicates the mean difference between sessions. Plots A and B demonstrate random error in agreement between ratings. AMT=active motor threshold

The test-retest reliability of the ECR for the whole group ranges from an ICC=0.590 (0.378, 0.743) for the AMT of the dominant limb to an ICC=0.710 (0.543, 0.823) for the RMT of the dominant limb. The lower end of the confidence interval falls within the range of poor reliability for most conditions. The 95% CI and 95% LOA are wide for all conditions indicating variability and imprecision in the measurement. The ICC values tend to be higher for the RMT compared to the AMT. The Bland-Altman plots demonstrate random error in agreement between tests. The line of mean difference falls close to zero (no change between tests) for the group as a whole.

Table 23 - Test-Retest Reliability ICC and LOA of the Motor Threshold for the Extensor Carpi Radialis Muscle

Muscle	Participant	Active/resting	Dominant/ non-dominant	ICC (95% CI)	Reliability Category	95% Limits of Agreement
ECR	Whole group n=51	Resting	Dominant n=50	0.710, (0.543, 0.823)	Moderate	-12.165 to 10.818
			Non-dominant n=51	0.688, (0.507, 0.810)	Moderate	-11.051 to 10.785
		Active	Dominant n=51	0.590, (0.378, 0.743)	Poor	-8.594 to 9.574
			Non-dominant n=51	0.670, (0.485, 0.798)	Poor	-8.246 to 8.735
ECR	< 50 y/o n=33	Resting	Dominant	0.702 (0.476, 0.841)	Poor	-12.714 to 10.390
			Non-dominant	0.665 (0.415, 0.882)	Poor	-10.811 to 10.296
		Active	Dominant	0.570 (0.288, 0.761)	Poor	-8.756 to 9.783
			Non-dominant	0.651 (0.398, 0.811)	Poor	-7.236 to 7.074
ECR	> 50 y/o n=18	Resting	Dominant	0.735, (0.420, 0.892)	Poor	-10.411 to 12.077
			Non-dominant	0.705, (0.360, 0.879)	Poor	12.386 to 12.986
		Active	Dominant	0.661, (0.293, 0.858)	Poor	-8.465 to 9.298
			Non-dominant	0.699, (0.352, 0.876)	Poor	-10.632 to 13.132
ECR	Women n=30	Resting	Dominant	0.675, (0.419, 0.832)	Poor	-12.422 to 11.564
			Non-dominant	0.569, (0.262, 0.773)	Poor	-12.529 to 12.279
		Active	Dominant	0.547, (0.241, 0.757)	Poor	-8.741 to 11.669
			Non-dominant	0.663, (0.396, 0.826)	Poor	-7.668 to 9.454
ECR	Men n=21	Resting	Dominant	0.740 (0.468 ,0.885)	Poor	-12.045 to 10.045
			Non-dominant	0.861 (0.654, 0.944)	Moderate	-9.379 to 9.094
		Active	Dominant	0.526 (0.127, 0.777)	Poor	-7.521 to 5.902
			Non-dominant	0.624 (0.275, 0.828)	Poor	-8.901 to 7.663

Muscle	Participant	Active/resting	Dominant/ non-dominant	ICC (95% CI)	Reliability Category	95% Limits of Agreement
ECR	Non-exercisers n=11	Resting	Dominant n=11	0.775, (0.363, 0.934)	Poor	-19.903 to 16.736
			Non-Dominant n=11	0.872, (0.569, 0.966)	Moderate	-11.402 to 10.402
		Active	Dominant n=11	0.565, (0.040, 0.856)	Poor	-9.566 to 12.232
			Non-Dominant n=11	0.759, (0.292, 0.930)	Poor	-9.198 to 11.198
ECR	Exercisers n=40	Resting	Dominant	0.663, (0.444, 0.807)	Poor	-8.868 to 8.112
			Non-Dominant	0.601, (0.357, 0.767)	Poor	-11.119 to 11.011
		Active	Dominant	0.589, (0.339, 0.760)	Poor	-8.297 to 8.729
			Non-Dominant	0.605, (0.370, 0.769)	Poor	-7.958 to 7.958

Table 23 - The reliability of the motor threshold of the bilateral ECR of the whole group and subgroups based on age, gender, and participation in exercise. Reliability was assessed using the ICC and LOA. The ICC model used was ICC[2,1] and the associated 95% CI acceptable reliability is an ICC > 0.70. The 95% LOA were determined using Bland and Altman's 95% lower and upper limits of agreement and difference between measurement was calculated session 1 minus session 2. The lower end of the confidence interval falls within the range of poor reliability for most groups, the estimated ICC values falls within the moderate to good range.ECR=extensor carpi radailis, ICC=intraclass correlation coefficient, CI=confidence interval, LOA=limits of agreement

Figure 35 - Bland Altman Plots of the RMT of the Extensor Carpi Radialis Muscle

A.

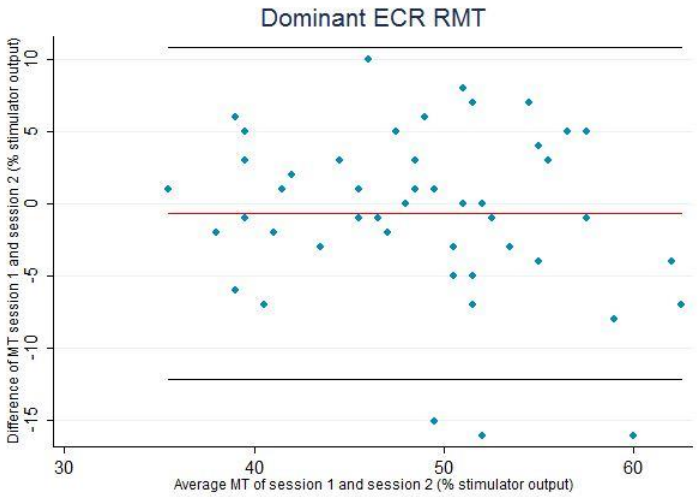


Figure 35 A. 95% LOA plot of RMT of the dominant ECR
n=50

B.

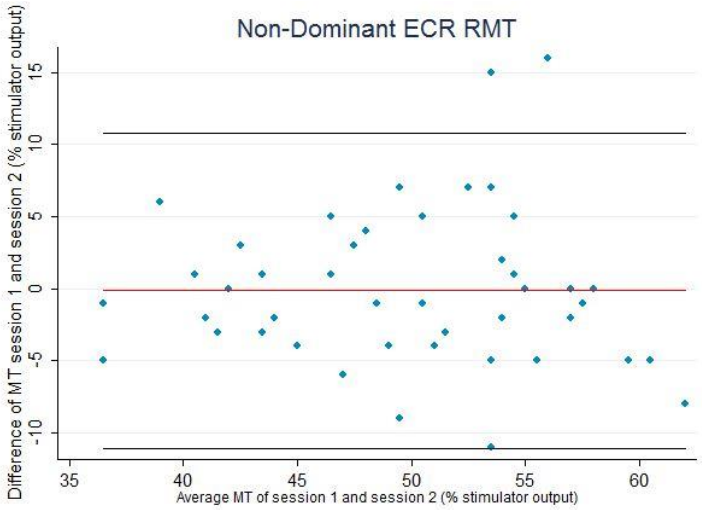


Figure 35B. 95% LOA Plot of RMT of the non-dominant ECR
n=51

Figure 35 A & B - Bland-Altman plots for the RMT of the ECR. The x axis is the average RMT of session 1 and 2 plotted against the difference in RMT between session 1 minus session 2, the red line indicates the mean difference between sessions. Plots A and B demonstrate random error in agreement between sessions. RMT= Resting motor threshold, ECR= extensor carpi radailis muscle

Figure 36 - Bland-Altman Plots of the AMT Extensor Carpi Radialis

A.

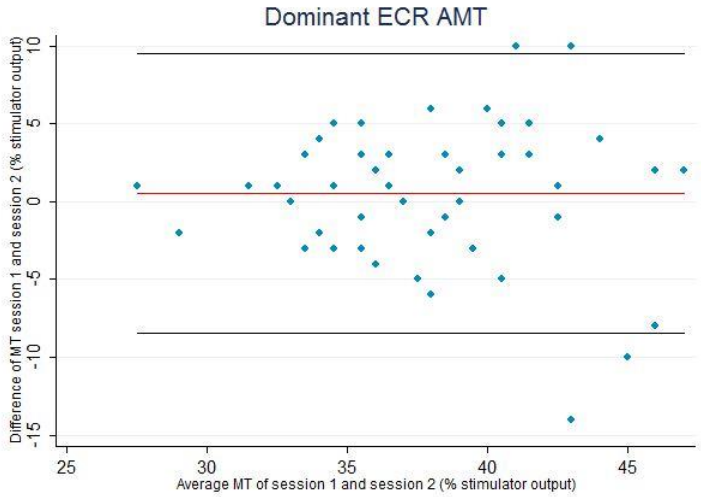


Figure 36 A. Bland-Altman plot of AMT of the dominant ECR n=51

B.

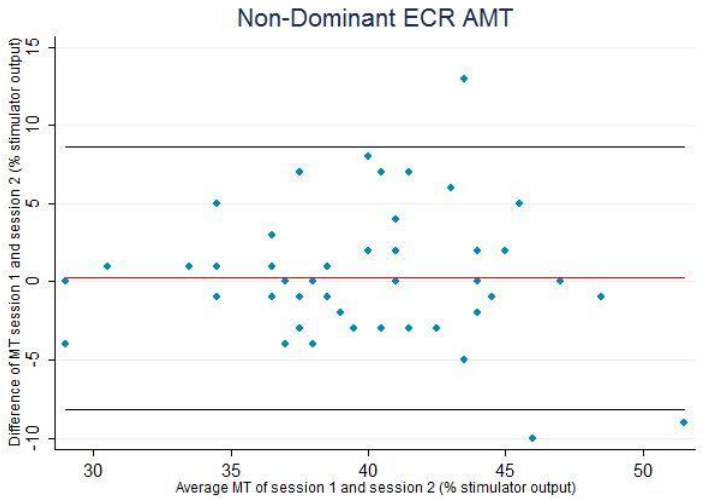


Figure 36 B. Bland-Altman plot of AMT of the non-dominant ECR n=51

Figure 36 A & B - Bland-Altman plots for the AMT of the ECR assessed during 20% MVC background contraction. The x axis is the average AMT of session 1 and 2 plotted against (y-axis) the difference in AMT between session 1 and session 2, the red line indicates the mean difference between sessions. Plots A and B demonstrate random error in agreement between sessions. RMT= Resting motor threshold, ECR= extensor carpi radailis muscle

The test-retest reliability of the APB for the whole group ranges from an ICC=0.547 (0.322, 0.714) for the AMT of the dominant limb to an ICC=0.693 (0.517, 0.813) for the RMT of the dominant limb. The lower end of the confidence interval falls within the range of poor reliability for most conditions. The 95% CI and 95% LOA are wide indicating variability and imprecision in TMS measurement. The RMT tends to exhibit higher ICC values than the active motor threshold. The Bland-Altman plots exhibit random error in agreement between sessions. The line of mean difference falls close to zero (no change between tests) for the group as a whole.

Table 24 - Test-Retest Reliability ICC and LOA of the Motor Threshold for the Abductor Pollicis Brevis

Muscle	Participant	Active/Resting	Dominant/ non-dominant	ICC (95%CI)	Reliability Category	95% Limits of Agreement
APB	Whole group n=51	Resting	Dominant n=51	0.693 (0.517, 0.813)	Moderate	-11.121 to 11.329
			Non-dominant n= 50	0.680 (0.498, 0.805)	Poor	-9.820 to 0.910
		Active	Dominant n= 51	0.547 (0.322, 0.714)	Poor	-9.102 to 9.959
			Non-Dominant n=51	0.556 (0.337, 0.719)	Poor	-7.976 to 9.893
APB	< 50 y/o n=33	Resting	Dominant	0.706 (0.484, 0.843)	Poor	-11.718 to 10.551
			Non-Dominant	0.658 (0.412, 0.815)	Poor	-9.916 to 9.674
		Active	Dominant	0.662 (0.414, 0.818)	Poor	-9.280 to 8.037
			Non-Dominant	0.561 (0.281, 0.755)	Poor	-7.408 to 8.519
APB	> 50 y/o n=18	Resting	Dominant	0.657 (0.279, 0.857)	Poor	-8.749 to 13.082
			Non-dominant	0.689 (0.338, 0.874)	Poor	-8.921 to 14.012
		Active	Dominant	0.123 (0, 0.544)	Poor	-5.842 to 13.176
			Non-dominant	0.457 (0,0.757)	Poor	-9.270 to 13.603
APB	Women n=30	Resting	Dominant	0.686 (0.434, 0.839)	Poor	-10.152 to 12.077
			Non-dominant	0.684 (0.428, 0.839)	Poor	-10.361 to 12.921
		Active	Dominant	0.527 (0.206, 0.745)	Poor	-9.776 to 11.419
			Non-Dominant	0.558 (0.252, 0.764)	Poor	-8.100 to 11.433
APB	Men n=21	Resting	Dominant	0.696 (0.381, 0.865)	Poor	-12.243 to 10.243
			Non-Dominant	0.683 (0.362, 0.858)	Poor	-8.729 to 7.887
		Active	Dominant	0.554 (0.163, 0.793)	Poor	-8.118 to 7.927
			Non-Dominant	0.555 (0.190, 0.789)	Poor	-7.528 to 7.623
APB	Non-Exercisers N=11	Resting	Dominant n=11	0.760, (0.316, 0.930)	Poor	-11.188 to 14.021
			Non-Dominant n=11	0.732, (0.250, 0.921)	Poor	-7.721 to 8.521
		Active	Dominant n=11	0.678, (0.151, 0.903)	Poor	-7.804 to 11.138
			Non-Dominant n=11	0.759, (0.334, 0.929)	Poor	-7.323 to 12.990

Muscle	Participant	Active/Resting	Dominant/ non-dominant	ICC (95%CI)	Reliability Category	95% Limits of Agreement
APB	Exercisers	Resting	Dominant n=40	0.663 (0.445, 0.807)	Poor	-11.109 to 10.442
	N=40		Non-Dominant n=40	0.669 (0.454, 0.811)	Poor	-10.456 to 11.632
		Active	Dominant n=40	0.480 (0.203, 0.687)	Poor	-9.512 to 9.566
			Non-Dominant n=40	0.477 (0.206, 0.682)	Poor	-7.934 to 8.600

Table 24 - The reliability of the motor threshold of the bilateral APB of the whole group and subgroups based on age, gender, and participation in exercise. Reliability was assessed using the ICC and LOA. The ICC model used was ICC [2, 1] and the associated 95% CI, acceptable reliability is an ICC > 0.70. The 95% LOA were determined using Bland and Altman's 95% lower and upper limits of agreement, the difference between tests was determined by session 1 minus session 2, The lower end of the 95% CI falls within the range of poor reliability for most measures. APB=abductor pollicis brevis, ICC=intraclass correlation coefficient, CI=confidence interval, LOA=limits of agreement

Figure 37 - Bland-Altman Plots of the Motor Threshold for the Abductor Pollicis Brevis

A.

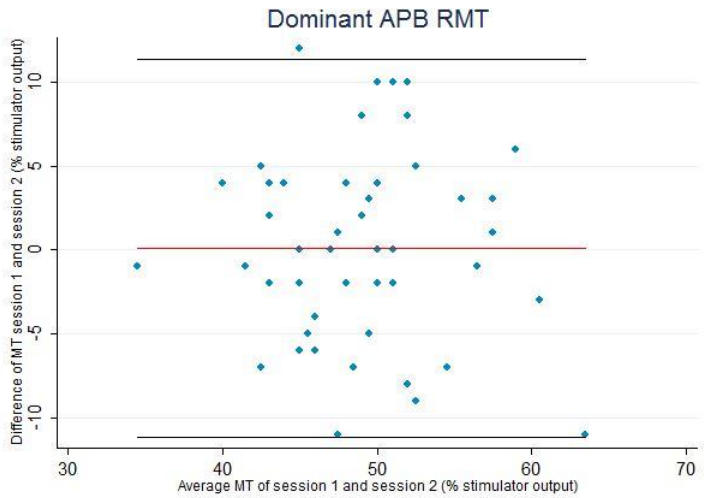


Figure 37 A. Bland-Altman Plot of RMT for the dominant APB n=51

B.

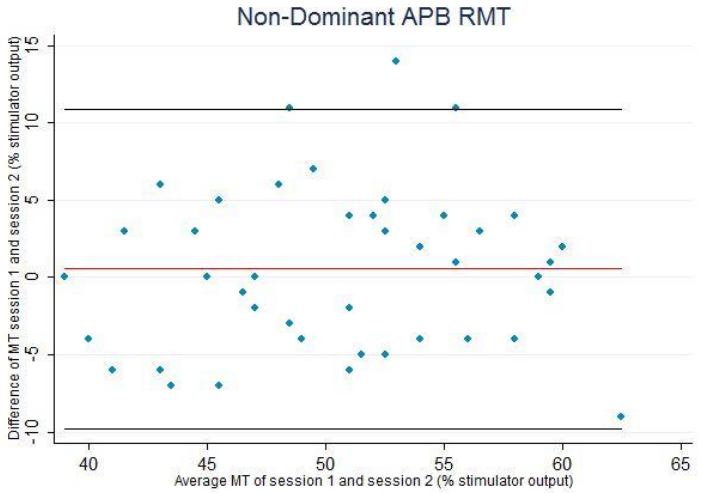


Figure 37 B. Bland-Altman Plot of the RMT for the non-dominant APB n=50

Figure 37A & B - Bland-Altman Plot of the RMT of the bilateral ABP. The x axis is the average RMT measured of session 1 and session 2 plotted against (y-axis) the difference in resting motor threshold between session 1 minus session 2. The red line is the mean difference between sessions. Plots A and B represent random error in agreement between sessions.

Figure 38 - Bland-Altman Plots of the Active Motor Threshold for the Abductor Pollicis Brevis

A.

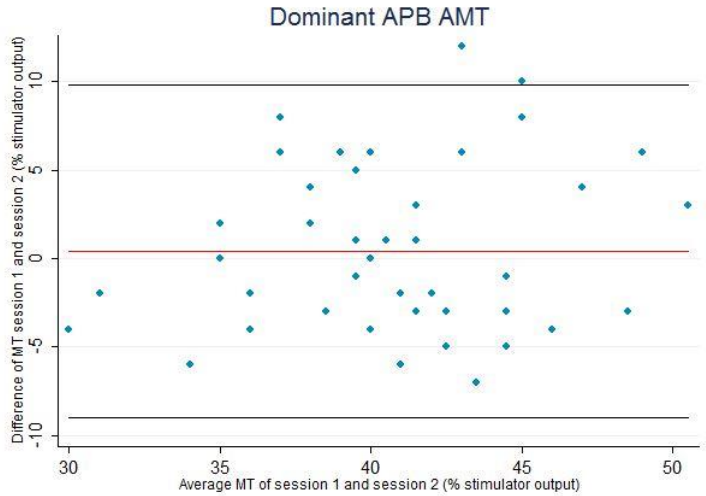


Figure 38 A. Bland-Altman Plot of AMT of the dominant APB n=51

B.

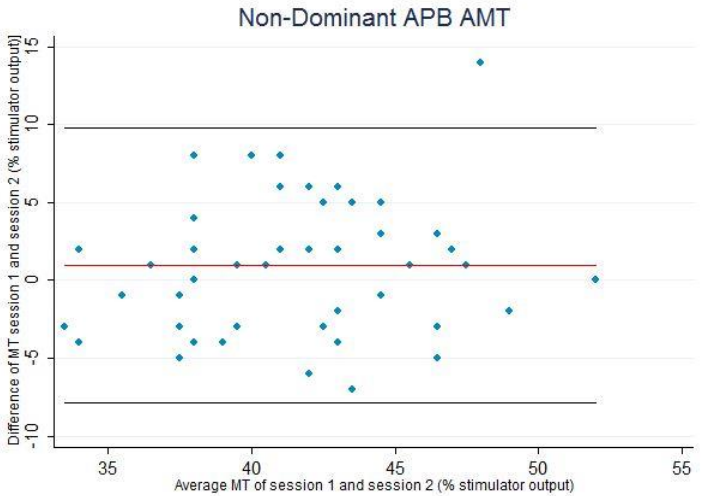


Figure 38 B. -Altman plot of AMT of the non-dominant APB n=51

Figure 38A & B - 95% LOA Plot (Bland-Altman Plot) of the AMT of the bilateral ABP. The x axis is the average AMT of session 1 and session 2 plotted against (y-axis) the difference in AMT between session 1 minus session 2. The red line is the mean difference between sessions. Plots A and B demonstrate random error in agreement between sessions. AMT= active motor threshold, APB=abductor pollicis brevis, LOA=limits of agreement

The 95% confidence intervals and 95% LOA were wide for all muscles indicating variability and imprecision in the measurement. The lower end of the confidence interval fell within the range of poor reliability for most muscles and conditions.

4.3.6.2 **Older and younger adults**

Younger and older adults demonstrated similar ICC values for the biceps muscle. The younger adults exhibited values of an ICC > 0.650 (0.394, 0.813) (RMT dominant biceps) and older adults exhibited values of an ICC > 0.651, (0.250, 0.857) (AMT dominant biceps), however older adults exhibited wider confidence intervals. Similar reliability and confidence intervals were found for both older and younger adults for the ECR, for example younger adults exhibited ICC values > 0.570 (0.288, 0.761) (AMT dominant ECR) and older adults exhibited ICC values > 0.661 (0.293, 0.858) (AMT non-dominant biceps). The older adults demonstrated wider confidence intervals compared to the group as a whole biceps dominant AMT ICC=0.651 (0.250, 0.857), whole group ICC=0.757 (0.612, 0.854). The younger adults demonstrated higher ICC values for the APB ICC values > 0.561 (0.382, 0.755) (AMT non-dominant APB). On the other hand, older adults demonstrated lower ICC values ICC > 0.123 (-0.338, 0.544) of the AMT for the dominant ECR.

4.3.6.3 **Women and men**

The sub-groups of men and women demonstrated similar ICC values for the motor threshold of the biceps, ECR and APB muscles, Table 22 to Table 24. For example, women demonstrate ICC > 0.666, (0.392, 0.831) for the RMT of the dominant biceps and men ICC > 0.655 (0.303, 0.848) RMT dominant biceps.

4.3.6.4 **Exercisers and non-exercisers**

Individuals who engaged in exercise demonstrated lower ICC values for the reliability of the APB and the ECR, compared to demonstrating greater ICC values for the biceps, Table 22 to Table 24. Exercisers demonstrated an ICC > 0.683, (0.469, 0.822) (RMT dominant biceps) compared to non-exercisers demonstrating lower values ICC > 0.570, (0, 0.864) (RMT dominant Biceps).

4.3.6.5 **Motor Evoked Potential amplitude**

The test-retest reliability (ICC and LOA) of the average MEP amplitude at 100%, 110%, 120%, and 130% of AMT is in Table 22 to Table 24 for the group as a whole; sub-group analysis is in Appendix 10. Example Bland-Altman plots are in Figure 39 and all Bland-Altman plots and Bland-Altman plots for all muscles are in Appendix 11.

During active conditions the reliability is variable ranging from ICC=0.126 (0, 0.377) for the dominant APB at 100% AMT to ICC=0.763 (0.618, 0.857) for the dominant ECR at 130% AMT. The lower end of the confidence interval falls within the range of poor reliability for most measures (excluding the dominant ECR 110%-130% AMT). The 95% CI and 95% LOA are wide, indicating variability in the measurement. The dominant ECR muscle exhibited the most consistent estimated ICC values (ICC > 0.70; estimated value) at 110%, 120%, and 130% of AMT.

The Bland-Altman plots demonstrate a potential association between MEP amplitude and agreement between sessions; as the average MEP amplitude increases the difference in amplitude between sessions also increases during resting and active conditions. Additionally, the mean difference for the group as a whole between sessions for the biceps is above the zero difference line suggesting the MEP amplitude was smaller at the second session; the line of mean difference for the ECR and APB fall close to zero (no difference between sessions).

Table 25 - Reliability ICC and LOA of MEP Amplitude 20% MVC Contraction All Participants

Muscle	% of AMT	ICC (95% CI)	95 % LOA	Reliability Category
Dominant Biceps	100	0.426, (0.173, 0.626)	-1.606 to 1.428	Poor
	110	0.465, (0.223, 0.654)	-2.168 to 1.533	Poor
	120	0.453, (0.209, 0.645)	-2.771 to 1.982	Poor
	130	0.499, (0.265, 0.678)	-3.091 to 2.289	Poor
Non-Dominant Biceps	100	0.539, (0.314, 0.707)	-1.599 to 1.876	Poor
	110	0.526, (0.299, 0.698)	-2.067 to 2.488	Poor
	120	0.626, (0.428, 0.767)	-2.141 to 2.665	Poor
	130	0.493, (0.258, 0.674)	-3.024 to 3.870	Poor
Dominant ECR	100	0.641, (0.445, 0.778)	-3.022 to 3.321	Poor
	110	0.747, (0.596, 0.848)	-2.824 to 3.069	Moderate
	120	0.759, (0.613, 0.855)	-2.878 to 3.026	Moderate
	130	0.763, (0.618, 0.857)	-2.860 to 2.925	Moderate
Non-Dominant ECR	100	0.510, (0.277, 0.687)	-1.887 to 1.615	Poor
	110	0.507, (0.270, 0.685)	-2.201 to 2.058	Poor
	120	0.556, (0.332, 0.720)	-2.062 to 2.166	Poor
	130	0.475, (0.230, 0.663)	-2.412 to 2.476	Poor
Dominant APB	100	0.126, (0,0.377)	-2.214 to 2.967	Poor
	110	0.441, (0.191, 0.638)	-2.783 to 3.092	Poor
	120	0.325 (0.053, 0.551)	-4.011 to 4.010	Poor
	130	0.306, (0.034, 0.536)	-4.498 to 4.163	Poor
Non-Dominant APB	100	0.459, (0.213, 0.652)	-3.179 to 3.787	Poor
	110	0.280, (0.011, 0.513)	-4.452 to 5.581	Poor
	120	0.506, (0.272, 0.685)	-3.929 to 5.282	Poor
	130	0.549, (0.324, 0.716)	-4.311 to 5.136	Poor

Table 25 - Reliability of average MEP amplitude assessed during 20% MVC at each interval of the recruitment curve of the bilateral biceps, ECR, and APB. The ICC model used was ICC [2, 1] and the associated 95% CI, acceptable reliability is an ICC > 0.70. The 95% LOA were determined using Bland and Altman's 95% lower and upper limits of agreement; the difference between sessions was determined as session 1 minus session 2. The lower end of the confidence interval falls within the poor range for most muscles for all intervals of the recruitment curve. AMT=active motor threshold, APB=abductor pollicis brevis, ECR=extensor carpi radialis, CI=confidence interval, ICC=intraclass correlation coefficient, LOA=limits of agreement

During resting conditions, the test-retest reliability of the average MEP amplitude is overall poor ICC < 0.50 . The 95% CI and 95% LOA are wide for all muscles indicating variability in the measurement.

Table 26 - Reliability ICC and LOA for the Average MEP Amplitude, Rest Conditions

Muscle	% of RMT	ICC (95% CI)	95% LOA	Reliability Category
Dominant Biceps	90	-0.056, (0, 0.225)	-1.198 to 1.861	Poor
	100	-0.058, (0, 0.218)	-1.927 to 2.727	Poor
	110	0.139, (0, 0.403)	-1.833 to 2.357	Poor
	120	-0.076, (0, 0.214)	-2.001 to 2.757	Poor
	130	-0.005, (0, 0.336)	-2.188 to 2.115	Poor
Dominant ECR	90	0.477, (0.230, 0.667)	-1.037 to 1.0468	Poor
	100	0.343, (0.075, 0.565)	-1.551 to 1.351	Poor
	110	0.457, (0.209, 0.650)	-1.814 to 1.571	Poor
	120	0.505, (0.264, 0.686)	-1.856 to 1.778	Poor
	130	0.491, (0.248, 0.676)	-1.690 to 1.811	Poor
Dominant APB	90	0.155, (0, 0.420)	-1.948 to 2.170	Poor
	100	0.302, (0.030, 0.535)	-2.144 to 2.695	Poor
	110	0.388, (0.125, 0.601)	-2.347 to 2.777	Poor
	120	0.190, (0, 0.446)	-3.520 to 3.859	Poor
	130	0.427, (0.159, 0.636)	-3.242 to 3.240	Poor

Table 26 - Reliability (ICC and LOA) of the average MEP amplitude assessed at rest; 90%, 100%, 110%, 120%, 130% of RMT. The ICC model used was ICC [2,1] and the associated 95% confidence intervals acceptable reliability is an ICC > 0.70. The 95% LOA were determined using Bland and Altman's 95% lower and upper limits of agreement; the difference between sessions was determined as session 1 minus session 2. The lower end of the confidence interval falls within poor reliability for all muscles. APB=abductor pollicis brevis, ECR=extensor carpi radialis, CI=confidence interval, ICC=intraclass correlation coefficient, LOA=limits of agreement, RMT=resting motor threshold

Figure 39 - Bland-Altman Plots of the Average MEP Amplitude

A.

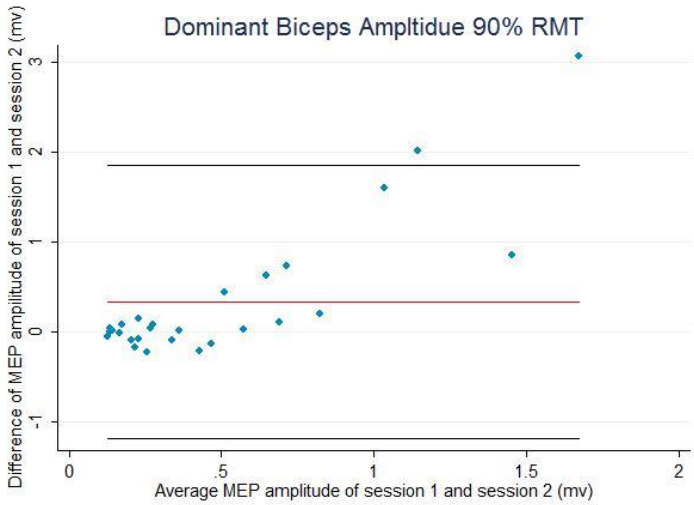


Figure 39 A. Bland-Altman plot of the average MEP amplitude of the dominant biceps assessed at 90% of RMT n=38

B.

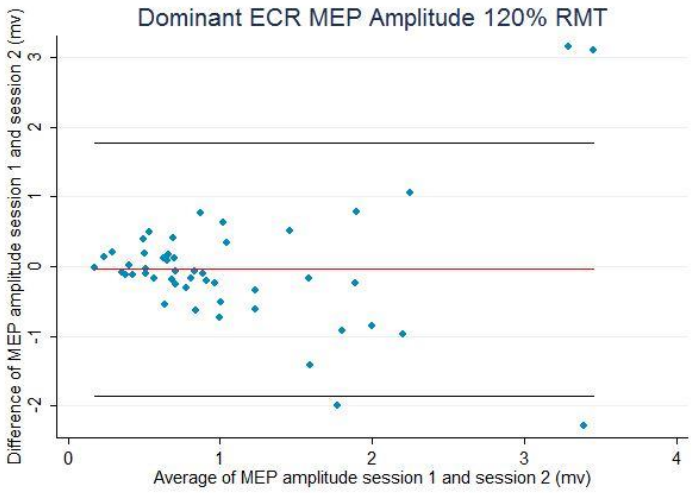


Figure 39 B Bland-Altman plot of the average MEP amplitude of the dominant ECR assessed at 120% RMT n= 49

Figure 39 A, B - Bland-Altman plot of the average MEP amplitude of the A) dominant biceps at 90% RMT, and B) dominant ECR assessed at 120% RMT. The x-axis represents the average MEP amplitude of session one and two, the y-axis represents the difference in MEP amplitude session one minus session two; the red line is the mean difference between sessions. Plots A demonstrates a trend towards a potential association such that the agreement between sessions is related to the magnitude of the measurement. Plot B suggests that as the MEP amplitude increases the difference between sessions also increases.

4.3.6.6 **Reliability of maximum motor evoked potential**

The reliability of the maximum MEP amplitude of all muscles is in Table 27, subgroup analysis is in Appendix 12. Example Bland-Altman plots are in Figure 40 and Bland-Altman plots for all muscles are Appendix 13.

The reliability of MEP max amplitude was generally poor, ranging from ICC=0.180 (0, 0.436) for the dominant biceps at rest to ICC=0.596 (0.385, 0.747) for the non-dominant biceps during active conditions. There were similar ranges of reliability for the ECR and the APB. The dominant ECR during active conditions demonstrated the highest ICC value ICC=0.781 (0.646, 0.869). The lower end of the confidence was in the range of poor reliability for all muscles and condition except the dominant ECR at rest. The 95% CI and 95% LOA were wide for all muscles and conditions indicating variability and imprecision in the measurement.

The Bland-Altman plots demonstrate random error in agreement between tests for the APB. The Bland-Altman plots for the ER and APB tend to demonstrate greater differences between sessions with larger MEP max amplitudes suggesting a possible association. The mean difference line for the group as a whole falls close to zero for all muscles (no difference between sessions).

Table 27 - Reliability (ICC and LOA) of the Maximum MEP Amplitude

Muscle	Number of Participants	ICC (95% CI)	95% LOA	Reliability Category
Dominant Biceps Rest	N=47	0.180 (0, 0.436)	-2.554 to 3.394	Poor
Dominant Biceps Active	N=51	0.574, (0.360, 0.732)	-3.243 to 2.501	Poor
Non-Dominant Biceps Active	N=51	0.596, (0.385, 0.747)	-2.968 to 3.957	Poor
Dominant ECR Rest	N=50	0.487, (0.242, 0.673)	-3.243 to 2.501	Poor
Dominant ECR Active	N=51	0.781, (0.646, 0.869)	-2.701 to 2.507	Moderate
Non-Dominant ECR Active	N=51	0.451, (0.199, 0.645)	-2.942 to 2.967	Poor
Dominant APB Rest	N=49	0.330, (0.053, 0.559)	-4.391 to 4.564	Poor
Dominant APB Active	N=51	0.380, (0.118, 0.592)	-4.907 to 4.522	Poor
Non-Dominant APB Active	N=50	0.581, (0.367, 0.738)	-4.421 to 5.349	Poor

Table 27-Test-retest reliability of the MEP max amplitude of the dominant and non-dominant biceps, ECR and APB muscles. The ICC was determined using model ICC [2,1] and associated 95% CI, acceptable reliability is an ICC > 0.70. The 95% LOA were determined using Bland and Altman's 95% lower and upper limits of agreement; the difference between sessions was determined as session 1 minus session 2. The lower end of the confidence interval was within poor reliability for all muscles except the dominant ECR. APB=abductor pollics brevis, ECR=extensor carpi radialis, CI=confidence interval, ICC=intraclass correlation coefficient, LOA=limits of agreement, MEP=motor evoked potential

Figure 40 - Bland-Altman Plot of MEP Max Amplitude of the Dominant ECR

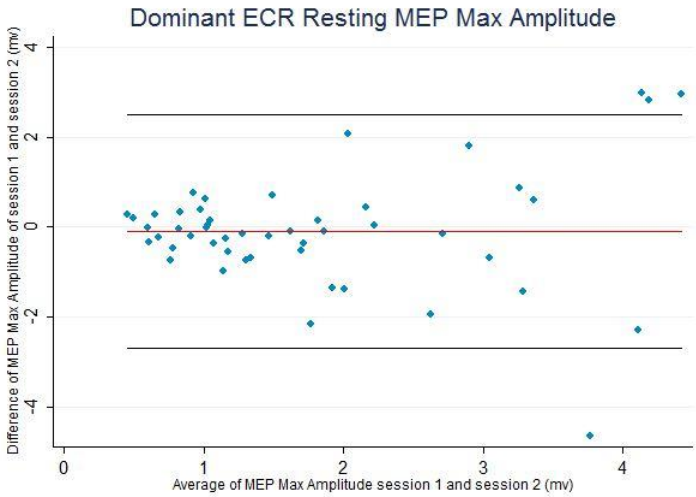


Figure 40-Bland-Altman plot of the dominant ECR MEP max amplitude assessed during resting conditions. The x-axis represents the average MEP max amplitude of session one and two, the y-axis represents the difference in MEP max amplitude of session one minus session two; the red line is the mean difference between session one minus session two. The plot demonstrates a trend towards larger differences between sessions with larger amplitudes. n=51

4.3.6.7 **Motor Evoked Potential Latency**

The test-retest reliability of MEP latency for each muscle was assessed at 120% and 130% of AMT, the results are in Table 28 and subgroups analysis is in Appendix 16. The MEP latency was also assessed at 120% of RMT and the results are in Table 29, sub-group analysis is in Appendix 15. Example Bland-Altman plots are in Figure 41, and Bland-Altman plots for all muscles are in Appendix 17.

The test-retest reliability during active conditions demonstrates variable reliability ranging from ICC=0.472(0.231, 0.660) for the dominant biceps at 130% AMT to an ICC=0.726 (0.560, 0.835) for the non-dominant APB at 130% AMT.

Table 28 - Reliability ICC and LOA of the MEP Latency during Active Conditions (120% AMT)

Muscle	120% AMT ICC (95% CI)	95% LOA	Reliability Category	130% AMT ICC (95% CI)	95% LOA	Reliability Category
Dominant Biceps	0.589 (0.375 to 0.743)	-2.708 to 2.603	Poor	0.472, (0.231, 0.660)	-4.141 to 3.303	Poor
Non-Dominant Biceps	0.614 (0.410 to 0.760)	-2.338 to 2.123	Poor	0.659, (0.473, 0.790)	-2.219to 1.816	Poor
Dominant ECR Active	0.653 (0.464 to 0.786)	-2.398 to 3.030	Poor	0.510, (0.275, 0.687)	-2.786 to 3.113	Poor
Non-Dominant ECR	0.560 (0.337 to 0.723)	-2.242 to 3.126	Poor	0.433, (0.185, 0.631)	-2.643 to 3.216	Poor
Dominant APB Active	0.563 (0.345 to 0.725)	-4.754 to 4.068	Poor	0.459, (0.212, 0.651)	-3.477 to 3.909	Poor
Non-Dominant APB	0.697 (0.523 to 0.815)	-3.388 to 3.512	Moderate	0.726, (0.560, 0.835)	-3.474 to 3.193	Moderate

Table 28 - The test-retest reliability of MEP latency assessed during active conditions (20% MVC) at 120%, and 130% of AMT of the bicep, ECR, and APB. The ICC was determined using model ICC [2,1], acceptable reliability is an ICC > 0.70. . The 95% LOA were determined using Bland and Altman's 95% lower and upper limits of agreement; the difference between sessions was determined as session 1 minus session 2. The lower end of the confidence interval is within the range of poor reliability for most muscles. AMT=active motor threshold, APB=abductor pollics brevis, ECR=extensor carpi radialis, CI=confidence interval, ICC=intraclass correlation coefficient, LOA=limits of agreement, MEP=motor evoked potential

The test-retest reliability during resting conditions (120% RMT) was also variable ranging from an ICC=0.436 (0.152 to 0.653) for the dominant biceps to an ICC=0.631 (0.426 to 0.774) for the dominant APB.

Table 29 - Reliability ICC and LOA of MEP Latency during Resting Conditions (120% of RMT)

Muscle	ICC	95% LOA	Reliability Category
Dominant Biceps Rest	0.436 (0.152 to 0.653)	-5.215 to 5.498	Poor
Dominant ECR Rest	0.492 (0.251 to 0.675)	-3.497 to 4.041	Poor
Dominant APB Rest	0.631 (0.426 to 0.774)	-4.228 to 4.278	Poor

Table 29 - The test-retest reliability of MEP latency assessed during resting conditions at 120% RMT. The ICC was determined using model ICC [2,1], acceptable reliability is an ICC > 0.70. The 95% LOA were determined using Bland and Altman's 95% lower and upper limits of agreement; the difference between sessions was determined as session 1 minus session 2. The lower end of the confidence interval is within the range of poor reliability for all muscles. APB=abductor pollics brevis, ECR=extensor carpi radialis, CI=confidence interval, ICC=intraclass correlation coefficient, LOA=limits of agreement, MEP=motor evoked potential

The 95% CI and 95% LOA were wide for both MEP latency assessed during active conditions and resting conditions indicating variability and imprecision in the measurement. The lower end of the confidence interval falls within the range of poor reliability for all muscles and conditions (resting and active) with the exception of the dominant APB during active conditions at 130% of AMT.

The Bland-Altman plots indicate random error in agreement between tests for all muscles (dominant and non-dominant) during resting and active conditions. The mean difference line for the group as a whole for the biceps falls slightly below zero suggesting a longer latency the second session, on the other hand the mean difference line for the ECR is slightly above zero suggesting a shorter latency the second session.

Figure 41 - Bland-Altman Plots of MEP Latency Assessed at 130% AMT of the ECR

A.

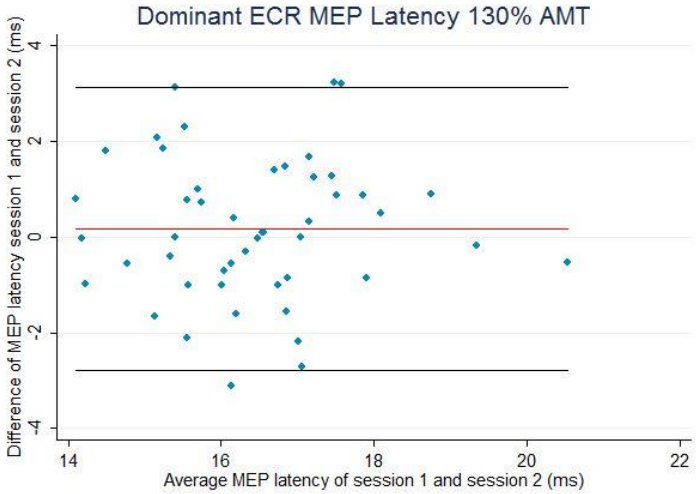


Figure 41 A. Bland-Altman plot of the dominant ECR MEP latency assessed at 130% of AMT n=50

B.

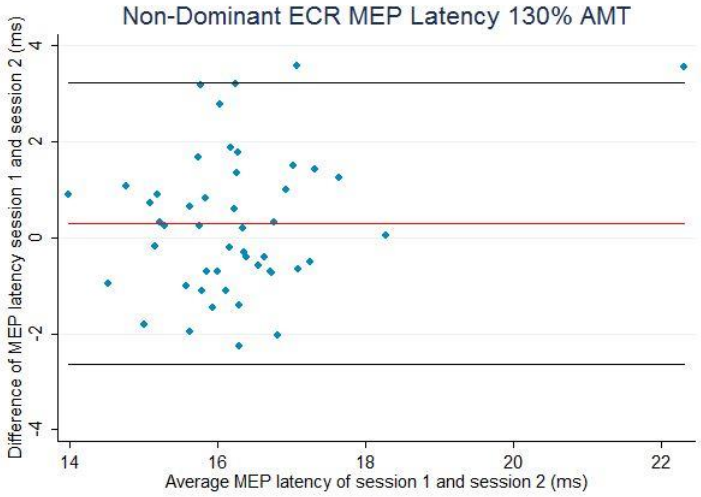


Figure 41 Figure 40B. Bland-Altman plot of the non-dominant ECR MEP latency assessed at 130% AMT n=51

Figure 41 A & B - Bland-Altman plots of the MEP latency of the A) dominant ECR and B) non-dominant ECR assessed at 130% AMT. The x-axis represents the average latency of session one and session two, the y-axis represents the difference in latency session one minus session two; the red line is the mean difference between sessions. Plots A and B represent random error in agreement between sessions.

4.3.6.8 **Silent Period**

The test-rest reliability of the silent period was assessed at 130% of AMT, the reliability of individual muscles is in

Table 30 sub-group analysis is in Appendix 14. Example Bland-Altman plots are in Figure 42 and Bland-Altman plots for all muscles are in Appendix 15.

The reliability was variable ranging from an ICC=0.537 (0.311, 0.706) for the non-dominant biceps to ICC=0.769 (0.589, 0.870) for the non-dominant APB. The lower end of the confidence interval was in the range of poor reliability for most muscles and conditions excluding the non-dominant ECR and non-dominant APB. The 95% CI and 95% LOA are wide for all muscles indicating variability and imprecision in measurement. The distal muscles demonstrate higher ICC values than the biceps.

The Bland-Altman plots demonstrate random error in agreement between tests for all muscles. The line of mean difference for the group as a whole for the biceps muscle and dominant APB is below zero suggesting a longer silent period the second session, for the ECR and non-dominant APB the mean difference line falls close to zero (no difference between sessions).

Table 30 - Reliability of the Silent Period assessed at 130% of AMT all Participants

Muscle	ICC (95%CI)	95% LOA (lower to upper limits)	Reliability Category
Dominant Biceps	0.614, (0.412, 0.759)	-47.343105 to 36.131371	Poor
Non-Dominant Biceps	0.537, (0.311, 0.706)	53.808777 to 46.421604	Poor
Dominant ECR	0.656, (0.465, 0.788)	-47.725487 to 46.062153	Poor
Non-Dominant ECR	0.750, (0.598, 0.850)	-52.759476 to 49.966129	Moderate
Dominant APB	0.647, (0.423, 0.791)	-61.976463 to 39.809525	Poor
Non-Dominant APB	0.769, (0.589, 0.870)	-69.658699 to 66.889076	Moderate

Table 30 - The reliability of the silent period assessed at 130% of AMT with 20% MVC background contraction (assessed individually for each participant at each session). The ICC was determined using model ICC [2,1], acceptable reliability is an ICC > 0.70 determined by the lower end of the confidence interval. The 95% LOA were determined using Bland and Altman's 95% lower and upper limits of agreement; the difference between sessions was determined as session 1 minus session 2. The lower end of the confidence interval is within the range of poor reliability for most muscles, additionally the 95% LOA are wide for all muscles. AMT=active motor threshold, APB=abductor pollics brevis, ECR=extensor carpi radialis, CI=confidence interval, ICC=intraclass correlation coefficient, LOA=limits of agreement, MEP=motor evoked potential

Figure 42 - Bland Altman Plots of the Silent Period

A.

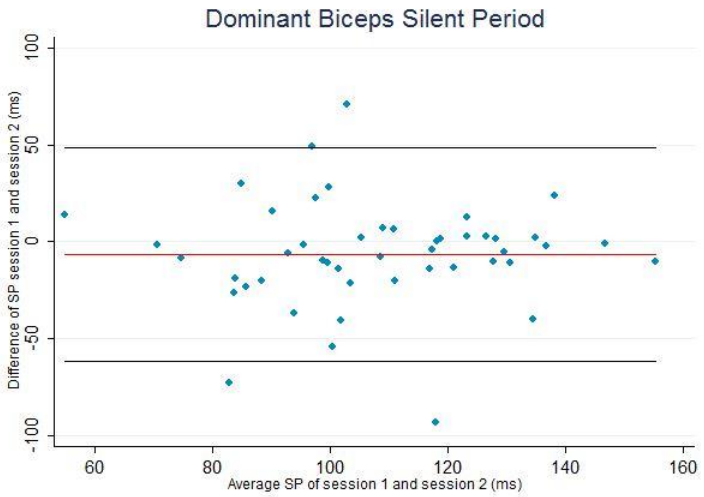


Figure 42A. Bland-Altman plot of the silent period of the dominant biceps muscle assessed at 130% AMT n=50

B.

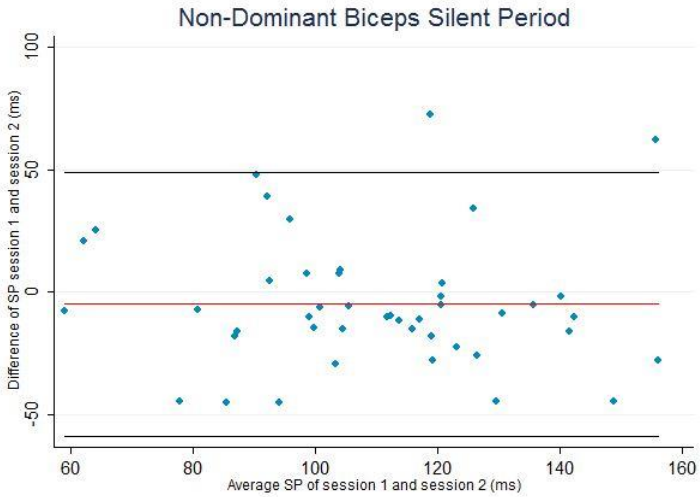


Figure 42B. Bland-Altman plot of the silent period of the non-dominant biceps muscle assessed at 130% AMT n=50

Figure 42A & B - Bland-Altman plots of the dominant biceps SP assessed at 130% of AMT. The x-axis represents the average SP between the two sessions and the y axis the difference in SP between the two sessions, the red line is the mean difference in SP between sessions. Plots A and B demonstrate random error in agreement between sessions. SP=silent period

4.3.7 **Recruitment Curve**

The test-retest reliability of the slope of the recruitment curve is in Table 31; example Bland-Altman plots are in Figure 43, and all Bland-Altman plots are in Appendix 18. The recruitment curve was fitted with a sigmoidal function; however the curve was not able to be fitted for all participants. The recruitment curve of the biceps was able to be fitted for 5/51 participants during resting conditions, 31/51 for active conditions; the ECR 15/51 for resting conditions, 23/51 for active conditions; and the APB 16/51 participants during resting conditions, and 29/51 for active conditions. Potential reasons the recruitment curve could not be fit for all participants was 1) not enough data points (less data points at high stimulation intensities because of uncomfortable stimulus) and 2) not all participants demonstrated an increase in MEP amplitude with increasing stimulus intensity (biceps rest n=7, active n=11, ECR rest n=7, active n=15, APB rest n=2, active n=19). Previous studies have also reported that not all participants data were able to be fitted with a sigmoidal function such as Schambra et al (2015) in which 5.9% of older adult participants did not fit a sigmoidal function and Massie and Malcolm (2013).

The test-retest reliability of the slope of the recruitment curve was poor for all muscles and all conditions ICC < 0.50.

The Bland-Altman plots demonstrate both random and systematic error in agreement between test occasions. The plot of the biceps muscle at rest demonstrates systematic error such that the second session had a lower slope.

The biceps muscle during active conditions and the dominant ECR during rest conditions tend to have a greater number of differences between sessions below the mean difference line, suggesting steeper slope on the second session. The Bland-Altman plot of the non-dominant APB suggests a possible linear association of the slope of the recruitment curve and the differences between sessions Figure 86. The line of mean difference for the group as a whole falls close to zero for the dominant ECR and dominant APB.

Table 31 - Test-Retest Reliability ICC and LOA for the Recruitment Curve

Muscle	Participants	ICC (95%CI)	95% LOA	Reliability Category
Dominant Biceps Rest	N=5	-0.017 (0, 0.816)	-1.270 to .873	Poor
Dominant Biceps active	N=16	0.031 (0, 0.487)	-0.640 to 0.938	Poor
Non-Dominant Biceps Active	N=15	0.052 (0, 0.503)	-0.390 to 0.628	Poor
Dominant ECR Rest	N=11	-0.116 (0, 0.521)	-3.058 to 3.412	Poor
Dominant ECR Active	N=11	-0.178 (0 0.459)	-3.266 to 4.197	Poor
Non-Dominant ECR Active	N=12	-0.009 (0, 0.553)	-7.048 to 5.539	Poor
Dominant APB Rest	N=16	0.026 (0, 0.480)	-1.313 to 1.971	Poor
Dominant APB active	N=16	-0.076 (0, 0.441)	-1.311 to 1.366	Poor
Non-Dominant APB	N=13	0.056 (0, 0.563)	-1.719 to 2.414	Poor

Table 31 - The test-retest reliability of the slope of the recruitment curve fitted with a sigmoidal function. The ICC was determined using model ICC [2,1], acceptable reliability was an ICC > 0.70. The 95% LOA were determined using Bland and Altman's 95% lower and upper limits of agreement; the difference between sessions was determined as session 1 minus session 2. The reliability is poor for all muscles

Figure 43 - Bland-Altman Plots of the Slope of the Recruitment Curve

A.

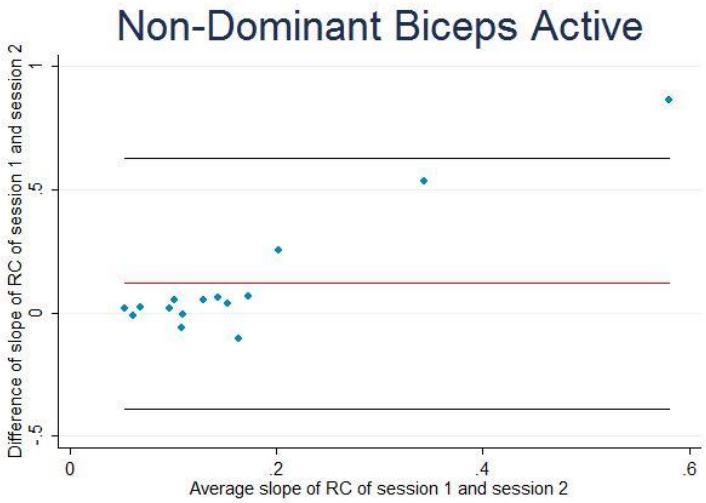


Figure 43 A. Bland-Altman plot of the recruitment curve of the non-dominant biceps muscle during background contraction of 20% MVC, n=16

B.

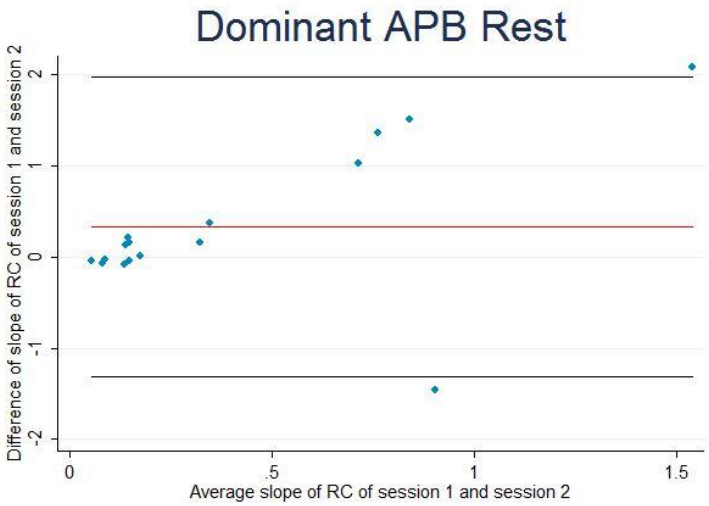


Figure 43 B. Bland-Altman plot of the recruitment curve of the dominant APB during resting conditions n=16

Figure 43 A & B - Bland-Altman plots of the recruitment curve of the A) dominant biceps muscle assessed during 20% MVC background contraction, and B) dominant APB during resting conditions. The x-axis is the average slope of the recruitment curve of session one and session two, the y-axis is the difference in slope of the recruitment curve of session one minus session two; the red line is the mean difference between session 1 minus session 2. Plots A and B demonstrate a possible linear association between the slope of the recruitment curve and the difference between sessions.

4.4 Discussion

In summary, the findings of this study indicate that the test-retest reliability of TMS measures of corticospinal pathway excitability are variable within individual MEP elements and among elements in this population. The lower end of the confidence interval was below the acceptable range of reliability (ICC < 0.70) for most measures. The wide confidence intervals and 95% LOA demonstrate lack of precision in the measurement. These findings suggest that TMS may not be suitable to detect change in corticospinal pathway excitability in individual participants. However, the Bland-Altman plots demonstrate that overall the line of mean difference for the group as a whole falls close to zero no difference between sessions. This suggests that TMS may be more suitable to evaluate groups of participants compared to individual differences in corticospinal pathway excitability.

4.4.1 MEP Elements

Overall, a majority of the MEP elements evaluated in this study were comparable to previous research. The ability to make direct muscle comparisons was not possible for all muscles and all MEP elements due to previous studies assessing different muscles, MEP elements and differing TMS methodology limiting comparisons between studies.

The mean motor thresholds for the APB in the present study (dominant limb: 49 ±7.07 (% of stimulator output), non-dominant limb: 51±6.77) are comparable to the findings by Corneal et al (2005) 48.46±14.07, but higher than other research using navigated (38±6) and non-navigated (39±5) TMS (Julkunen et al., 2009). Of note the age of participants in the study by Julkunen (2009) was not reported and thus the findings may not be comparable. The motor threshold of the ECR 48±6.87 to 50±6.90 is comparable to previous work yielding a motor threshold of 51.73±6.6 to 53.67±8.9 (Kossev et al., 2002).

The MEP amplitude of the APB in the present study assessed at motor threshold ranged from 1.06 ±0.55 mV for the non-dominant APB to 1.97±1.88 mV for the dominant APB at 100% AMT. The smaller MEP amplitudes found in this study are similar to earlier research exhibiting an APB amplitude of 1.13±0.80 mV (non-navigated TMS) (Julkunen et al., 2009). Of note the present study assessed amplitude during 20% MVC whereas Julkunen et al (2009) assessed the amplitude at rest which may explain the larger end of the range of amplitudes identified in in this study (1.97±1.88 mV). It is known that background muscle contraction increases MEP amplitude (Di Lazzaro et al., 2004) and thus may contribute to the differences identified. The amplitude of the first dorsal interosseous (FDI) another thenar muscle was comparable to the present study demonstrating an amplitude of 2.1±1.8 mV in women and 1.7±1.2 mV in men (Pitcher et al., 2003).

In general the MEP latencies in the present study are in line with previous research. The MEP latency of the APB in the present study (22.24±2.38 to 23.65±2.76 ms) for the APB is comparable to the latency exhibited by Julkunen et al (2009) (22.9±1.2 ms); however the standard deviation is greater in the present study. The latency of the biceps muscle is comparable to work by Furby et al (1992) yielding latencies of 12.5±1.1 ms with slight contraction to 14.4±1.4 ms at rest (Furby et al., 1992). Alternatively, the biceps latency in this study is 2-3 ms slower than others (Eisen and Shtybel, 1990). The ECR latency identified in this study (16.08±1.21ms to 17.90±1.51 ms) is comparable to earlier findings (16.96±1.27 ms to 17.56±0.93 ms) (Kossev et al., 2001).

The closest comparison for the silent period of the APB is a study by Koski in which the silent period of the FDI was investigated. The silent period in the present study was about 20 ms longer (118±32 ms) than the study by Koski et al (2005). However, the study by Koski and colleagues (2005) assessed the silent period during 10% MVC and at 105% of MT whereas in the present study the silent period was assessed during 20% MVC and at 130% of MT thus direct comparisons cannot be made. There is evidence that the as the strength of the TMS stimulus increases the length of the silent period also increases (Orth and Rothwell, 2004, Säisänen et al., 2008, Inghilleri et al., 1993) which may contribute to the longer silent period found in this study.

4.4.2 **Reliability of MEP elements**

The reliability of the motor threshold of the APB found in the present study is similar to the findings by Solloman and colleagues (2013) demonstrating a Lin's concordance correlation coefficient,(CCC) of 0.709 to (0.244, 0.909) (Sollmann et al., 2013). The biceps MEP amplitude and motor threshold ICC point estimate are similar to findings by Sankarasubramanian et al (2015) demonstrating motor threshold ICC= 0.745, MEP amplitude ICC=0.163. The present study demonstrated lower ICC values compared to previous research of upper limb muscles for most other measures such as MEP amplitude, silent period, and MEP latency (Carroll et al., 2001, Koski et al., 2005, Christie et al., 2007, Liu and Au-Yeung, 2014, Ngomo et al., 2012, Schambra et al., 2015).

The older adults exhibited similar ICC values to younger adults on most MEP elements with the exception of the ECR MEP amplitude in which older adults demonstrated higher ICC values. Additionally, older adults demonstrated wider confidence intervals when compared to younger adults suggesting greater variability an imprecision in measurement. Of note there were a larger number of participants 49 years of age and younger (n=34) which may have also contributed to the differences in confidence intervals. The ICC values of older adults in comparison to previous studies are comparable for the ICC of the slope of the recruitment curve (Schambra et al., 2015); and lower for the ICC of the motor threshold (Schambra et al., 2015) and MEP amplitude

(Christie et al., 2007). There were differences in TMS methods used between the studies which may have contributed to differences in ICC values. For example, neuro-navigated TMS was utilized by Schambra (2015) and a different coil location was used by Christie (2007). The age threshold used to determine an "older adult" was quantified differently. For example, Schambra and colleagues (2015) included participants ≥ 40 years of age, Christie and colleagues (2007) included participants ≥ 65 years of age; and this study designated participants' ≥ 50 years of age as older adults. There is evidence that from about age 50 age-related changes begin within the CNS and corticospinal pathway (Sullivan et al., 2010). Finally, the two studies investigating the reliability of TMS measures in older adults investigated the abductor digiti minimi and first dorsal interosseous respectively, whereas the present study investigated the biceps, ECR and APB. There is limited comparable research in the reliability of TMS measures in older adults.

The reliability of TMS measures for the group as a whole varied within and between MEP elements based on the target muscle of investigation. These findings of varied reliability for different muscles is similar to previous test-retest reliability research (Carson et al., 2013, Kamen, 2004, Malcolm et al., 2006). This finding is not surprising as there is evidence that the muscles of the upper limb respond differently to brain stimulation and demonstrate different reliability (Martin et al., 2006, Malcolm et al., 2006). There are additional factors that can influence reliability such as background muscle contraction, type of coil, direction of current, and physiological processes that will be discussed in detail in Chapter 6.

The lifestyle and environmental factors questionnaire highlighted that 44/51 participants consumed caffeine, 40/51 participated in exercise, 20/51 took prescribed medication, 1/51 participants smoked and 47/51 were right handed. There is evidence that these factors can influence neural plasticity and corticospinal pathway excitability (Specterman et al., 2005, Cerqueira et al., 2006, McGregor et al., 2011, Grundey et al., 2012). These factors were not controlled for in the study as the study was designed to be pragmatic. It is likely that a group of stroke survivors would also have participated in exercise, or consumed caffeine prior to the stroke or before their TMS session. Previous studies have documented their participants caffeine intake at 0.7±0.6 cups and 23.6±15.4 minutes of exercise (Schambra et al., 2015). Collecting information regarding lifestyle and environmental factors that can influence brain stimulation studies is pertinent to understanding the reliability of TMS without controlling for the factors.

4.4.3 **Strengths**

TMS measures were collected during resting conditions and during background muscle contraction. Research in non-neurologically intact populations such as stroke commonly utilise background muscle contraction to facilitate an MEP during data collection. Maintaining a contraction during TMS is beneficial in stroke survivors for a few reasons:

1) It is easier to determine a motor threshold (the corticospinal pathway is already stimulated by the contraction).

2) Stimulation may be more comfortable because a lower TMS stimulus is needed during muscle contraction.

3) More data points may be able to be collected for a recruitment curve if the threshold is lower

4) Decreased fluctuation in corticospinal pathway excitability

5) Standardisation of attention across all participants

It is beneficial to have normative reliability data that was collected with a background contraction in older adults for comparison with stroke survivors.

4.4.4 **Limitations**

The TMS methods used within this study may result in the findings not being comparable to other studies that utilised different methodologies. TMS data was collected during background muscle contraction which may not be comparable to earlier studies in neurologically intact adults in which TMS data is collected at rest. TMS data was collected at rest in the dominant limb only; this is in line with previous TMS research. However, limiting the data collected on the non-dominant limb which may respond differently to TMS.

The amount of arm use prior to the TMS session was not restricted nor was it recorded. There could have been varying levels of corticospinal pathway excitability prior to each session.

There was not 100% agreement of the two raters for the MEP latency. The raters were in agreement 84% of the time, despite the variability the latencies identified in this study were generally comparable to previous research (Julkunen et al., 2009, Furby et al., 1992, Eisen and Shtybel, 1990, Kossev et al., 2001). Because the MEP latency was variable before investigating the test-retest reliability, the inherent variability could have influenced the reliability, contributing to lower reliability and wide confidence intervals and 95% limits of agreement.

The recruitment curve was not able to be fitted for all participants, thus the analysis of test-retest reliability of the slope of the recruitment curve was underpowered.

4.4.5 **Conclusion**

This study determined that, within the population assessed, the test-retest reliability of TMS measures is variable, as well as demonstrating wide 95% CI and 95% LOA suggesting imprecision in TMS measurement. Further investigation in the reliability of TMS measures and methods of data collection is desirable.

5 Test-retest reliability of TMS measures of corticospinal pathway excitability early after stroke

5.1 Introduction

Transcranial magnetic stimulation (TMS) is being increasingly used as a clinical neurophysiology measure in stroke research to assess the connection between the motor cortex and the muscles of the arm and hand via the corticospinal pathway (Brouwer and Schryburt-Brown, 2006, Talelli et al., 2006, Park et al., 2004, Sawaki et al., 2008). Transcranial magnetic stimulation has been used in stroke rehabilitation research as an overall measure of excitability of the corticospinal pathway (or extent of damage) (Talelli et al., 2006), a measure of neural plasticity in response to a physical therapy intervention (Koski et al., 2004, Park et al., 2004, Sawaki et al., 2008), as a predictor of upper limb functional outcomes (Delvaux et al., 2003, Stinear et al., 2012), and repetitive TMS has been used as a priming therapy to promote neural re-organization (Dimyan and Cohen, 2011, Talelli et al., 2006). There is evidence that the degree of damage to the corticospinal pathway is correlated with motor recovery; for example the lesser the damage to the pathway the better the motor function and recovery outcome (Feydy et al., 2002, Ward and Cohen, 2004, Talelli et al., 2006, Wenzelburger et al., 2005). Developing a better understanding of the corticospinal pathway (via TMS measurement) can provide knowledge of the contribution of the corticospinal pathway to movement, motor control, and assess neural plasticity. This knowledge can be used to inform the development of interventions and assess the neural response to current and developing interventions.

The use of TMS in stroke research in the first few months after stroke is becoming more commonplace (Huynh et al., 2013, Manganotti et al., 2008, Stinear et al., 2012). TMS is being used in acute stroke to predict upper limb function (Stinear et al., 2012), to assess longitudinal neural plasticity in the first three months after stroke (Huynh et al., 2013), and to investigate long-term potentiation (LTP) like processes (Di Lazzaro et al., 2010). The use of TMS early after stroke is providing valuable information for clinical decision-making. An important aspect of measurement is agreement in the measurement when taken on separate occasions in which the individuals being assessed are not expected to change, test-retest reliability. Furthermore it is important that a measurement tool be reliable within the population it is being used to have confidence in the results to make appropriate clinical decisions. An example of an important clinical decision based on TMS is the presence or absence of a motor evoked potential (MEP) early after stroke,

which is being used as a predictor motor recovery (Stinear et al., 2012). However, previous research of the test-retest reliability of TMS measures has focused on investigations in people who are at least six months after stroke (chronic stroke) (Koski et al., 2007a, Liu and Au-Yeung, 2014, Cacchio et al., 2011). The results of the test-retest reliability in stroke survivors six months after stroke are variable and range from poor to good in the upper and lower limbs. The test-retest reliability findings in stroke survivors later after stroke may not be applicable to those earlier after stroke. The reliability findings of the individual studies can be found in Section 1.15.2 Table 5 page 61. The reliability of the motor threshold and silent period demonstrate more consistent reliability; intraclass correlation coefficient (ICC) ranging from ICC=0.57 of the biceps (Harris-Love et al., 2013) to ICC=0.97 (0.94 to 0.99) for the FDI (Liu and Au-Yeung, 2014). The MEP amplitude demonstrated the most variable findings, ICC values ranging from ICC=0.205 in the vastus lateralis (Cacchio et al., 2011) to an ICC= 0.98 (lower level of the 90% confidence interval 0.94) in the (first dorsal interosseous) FDI muscle (Koski et al., 2007a). The difference in reliability of the biceps and FDI may be due to the different corticospinal projections to the proximal and distal upper limb muscles (Martin et al., 2006). The reliability findings later after stroke may not be applicable to stroke survivors early after stroke because there are physiological differences in the nervous system early after stroke (within the first three months) compared to later after stroke (> 6 months).

The physiological differences early after stroke within the central nervous system are: the initial inflammatory response to stroke (Wahl and Schwab, 2014), spontaneous recovery, (Cramer, 2008), hyperexcitability of motor areas (Marshall et al., 2000, Calautti et al., 2001) and task-specific re-organization through participation in rehabilitation (Buma et al., 2013). Neural plasticity continues in the chronic stages of recovery however at a slower rate (Wahl and Schwab, 2014), and is more likely due to task-specific re-organization. It is thought that the physiological processes happening within the central nervous system (CNS) contribute to accelerated motor recovery early after stroke (Wahl and Schwab, 2014, Kwakkel and Kollen, 2013, Langhorne et al., 2011). The accelerated motor recovery may be associated with accelerated changes in corticospinal pathway excitability and neural plasticity measured using TMS.

There is reason to believe there may be variability in corticospinal pathway excitability early after stroke due to spontaneous recovery, hyperexcitability, and the potential accelerated rate of neural plasticity in the acute and sub-acute phases of stroke recovery. The reliability of TMS measures in stroke survivors later after stroke may not be applicable to those early after stroke. It is unknown how this rapid rate of neuroplasticity may influence corticospinal pathway excitability and the reliability of TMS

measurement. It is important to determine the reliability of TMS measures in stroke survivors early after stroke, as TMS is being increasingly used within this population.

The aim of this study is to answer research question number three: “Is TMS measurement of the coritcospinal pathway reliable in a group of sub-acute stroke survivors?” The study will determine the test-retest reliability of TMS measures of coritcospinal pathway excitability such as active and resting motor threshold, motor evoked potential amplitude, motor evoked potential latency, silent period, and a recruitment curve of both the more-affected and less-affected biceps brachii, extensor carpi radialis and abductor pollicis brevis muscles in a group of stroke survivors who are 2-60 days after a stroke.

5.2 Methods

5.2.1 Ethics and informed consent

Ethical approval for this project was obtained from the NRES Committee East of England-Norfolk as a substantial amendment to the FAST INdICATE randomized clinical trial which was ongoing. The IRAS project ID is 79063, REC reference number is 11/EE/0524. The ethical approval letters can be found in Appendix 19. This study was conducted in accordance with the Declaration of Helsinki. Separate additional informed consent from the FAST INdICATE trial consent was obtained for each participant prior to participation in this study.

At the conclusion of the baseline FAST INdICATE session participants were given a participant information sheet detailing the purpose and procedures of the study. Participants were then given at least 24 hours to decide if they wanted to take part. Interested participants then returned to the research lab for the additional TMS session. When participants arrived for the additional session of TMS the TMS procedures were reviewed and all questions answered to the person's satisfaction. Separate written informed consent was obtained before initiating TMS. If a participant was unable to write, they could choose an independent witness to complete the form as the participant gave their verbal consent to participate in the study. An independent witness was not part of the research team, or managed by a member of the research team. The original signed consent was kept in the research file, one copy was kept in the participant's medical notes, and a third copy was given to the participant.

Data was collected and stored on a password protected computer that only the researcher and her supervisors had access to.

5.2.2 Research design

This study is a prospective correlational test-retest reliability design. This study was embedded within a larger randomized controlled trial, the FAST INdICATE trial. The FAST INdICATE trial is investigating how stroke survivors respond to functional strength training and movement performance therapy in the first months after stroke. The measurement battery of the FAST INdICATE trial comprises clinical observational measures, the Action Research Arm Test, Wolf Motor Function Test, hand dynamometry, the EQ-5D, neuroimaging using functional magnetic resonance imaging (fMRI), and non-invasive brain stimulation using TMS Table 32. The aim of the fMRI and TMS within FAST INdICATE is to investigate the neural correlates of improved upper limb motor function in response to functional strength training and movement performance therapy. The test-retest reliability was assessed over two identical TMS sessions; the baseline FAST INdICATE TMS session and an additional TMS session.

The two TMS sessions were separated by one to three days. The time frame of one to three days was selected based on several factors. The reliability was being investigated in a group of participants within the first 3 months after stroke which is the time of most rapid spontaneous recovery and neural plasticity (Cramer, 2008). All participants were actively participating in a rehabilitation program during the TMS assessments, and neural plasticity can be enhanced through participation in rehabilitation and reflected in TMS measurement (Buma et al., 2013, Koski et al., 2004) The neural plastic changes occurring due to spontaneous recovery and rehabilitation driven recovery can be reflected in the TMS measurement (Koski et al., 2004). The short time span of one to three days between testing sessions was chosen to limit the influence of neural plasticity on the TMS measurement.

5.2.3 **Participants and recruitment**

The participants were recruited from the FAST INdICATE trial. The inclusion criteria for this study were identical to the inclusion criteria for the FAST INdICATE trial with the addition of: the participant must be able to participate in TMS, all inclusion criteria are in

Box 1. Participants' suitability to participate in TMS was assessed via a health screening questionnaire which can be found in Appendix 8. The health screening questionnaire included questions that necessitated a yes or no answer. The questions addressed the contraindications to TMS including: implanted metal in the head, epilepsy, syncope, implantation of a device (cochlear implant, nerve stimulator, or hydrocephalus shunt, drug infusion pump), and any previous surgery to the head, neck or spine (Rossi et al 2009). If the answer to all the questions was 'no' than the person was able to participate in TMS.

Recruitment from the FAST INdICATE trial occurred at the baseline assessment, Figure 44 shows the recruitment process. The baseline assessment for the FAST INdICATE trial included completion of the Action Research Arm Test (ARAT), Wolf Motor Function Test (WMFT), EQ-5D, with the addition of TMS and fMRI if participants were suitable, a brief description of each assessment can be found in Table 32. At the conclusion of the baseline TMS assessment for the FAST INdICATE trial participants were invited to participate in this study; involving one additional session of TMS identical to that which was completed at the baseline FAST INdICATE assessment. The rationale and purpose of this study was explained and participants were given a Participant Information Sheet (Appendix 20) which further detailed the study purpose and procedures. Any questions participants had were answered. Participants were then given at least 24 hours to read over the Participant Information Sheet and decide if they wanted to take part in the study. Participants were called at home or visited by the researcher in the rehabilitation unit after the twenty-four hour period to inquire if they were interested in participating. Those participants who were interested in taking part in the study attended an additional TMS session within three working days of the baseline TMS assessment.

Participants were not age-matched to participants in Chapter 4 (reliability of TMS in neurologically intact adults) as the studies were run in parallel and recruitment for this study was dependent on the FAST Indicate trial. A more detailed explanation is in Chapter 4 Section 2.3.4 on page 115.

Box 1 - Inclusion Criteria for the FAST INdICATE Trial

Inclusion Criteria for FAST INdICATE

- Adult > 18 years of age
- 2-60 days post stroke when informed consent is obtained
- Cerebral Infarction in anterior cerebral circulation territory, cortical and/or subcortical, confirmed by neuroimaging
- Sufficient voluntary muscle contraction in the paretic upper limb to generate the beginning of prehension (for example a score of at least 11/33 on the Motricity Index pinch section)
- Unable to complete the Nine Hole Peg Test in 50 seconds or less (max time for test)
- No obvious motor dyspraxia or communication deficits as assessed by the ability to imitate action with the non-paretic upper limb. The accuracy of imitation of observed activity will be assessed on the 3-point scale used by Decety: 2=correctly reproduced action, 1= incorrectly reproduced action, 0=not reproduced. Those scoring greater than or equal to 8/10 will be considered to have the ability to imitate and included in the trial
- Prior to the stroke participants were able to use the paretic upper limb to lift a cup and drink from it

Additional Inclusion Criteria to participate in Reliability of TMS

- Suitable to participate in TMS assessed through a medical screening questionnaire Appendix 8.

Box 1 - Inclusion and exclusion criteria used to determine suitable participants for the FAST INdICATE trial and TMS.

5.2.3.1 **Power Calculation**

A power calculation was completed to achieve an ICC=0.8 with a CI of 0.7 to 0.9, 51 participants will be recruited. An ICC of 0.8 was selected based on previous findings of TMS reliability (Cacchio et al., 2009, Cacchio et al., 2011, Koski et al., 2007b, Portney and Watkins, 2009). A confidence interval of 0.7 to 0.9 was selected such that the lower end of the confidence interval 0.70 would be within the range of acceptable reliability ICC >0.70 (Portney and Watkins, 2009, de Vet et al., 2006).

Figure 44 - Recruitment Procedures

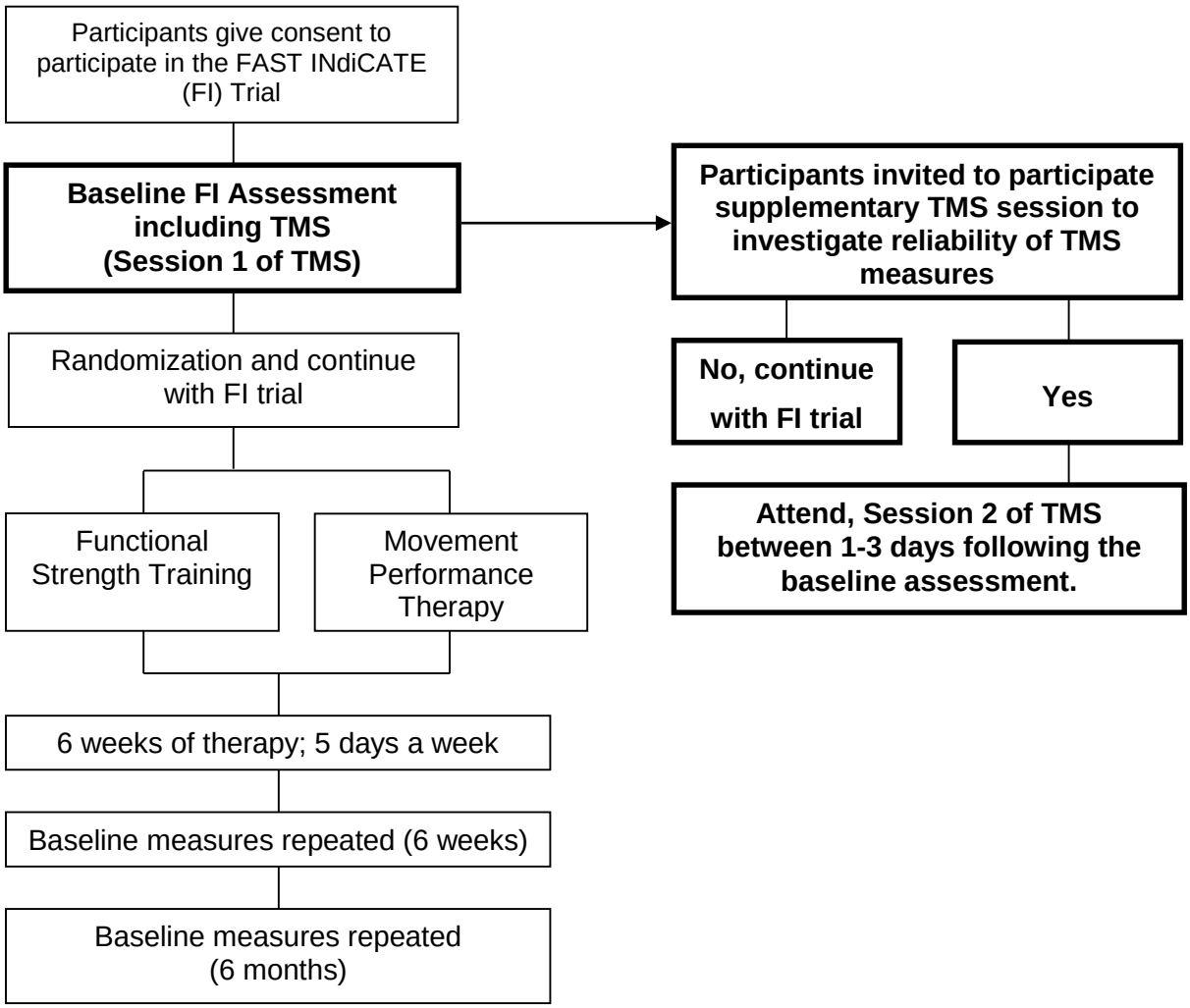


Figure 44 - Flow diagram representing the process of recruiting participants from the FAST INdICATE trial to the TMS reliability study. Participation in the TMS reliability study had no impact on the participants' participation in the rest of the trial.

Table 32 -Tests included at the Baseline Session of the FAST INdICATE Trial

Test	Description	Interpretation of Results
ARAT (Action Research Arm Test)	Observational test comprising 19 items assessing grasp, grip, pinch and gross arm movement. Participants have to grasp different sized and shaped objects (blocks, tubes, ball bearings, cup, and marbles) and transfer them to another surface (elevated shelf).	Scoring is from 0 to 3; 0 = cannot perform and 3 = performs test normally. The maximum score is 57 points. Higher scores indicate better upper limb function.
Wolf Motor Function Test WMFT (Wolf Motor Function Test)	Quantitative test comprising 21 timed functional tasks, in which movement quality is analysed. Participants have to grasp different functional objects (can, pencil, paperclip, checkers, towel, key and basket) and move the arm in various positions such as elbow extension, and placing the arm on an elevated shelf.	Each task is timed and participants are allowed up to 120 seconds to complete the task. Scoring is on a scale from 0-5; 0 “does not attempt with the involved arm” to 5 “arm does participate; movement appears to be normal”
EQ-5D	Standardized measure of health outcome assessing 5 domains, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The participants then rate their health state from 0-100.	Participants score each domain with “no problems”, “some problems”, or “unable”. The higher the participants rate their health state the better they view their health state.
TMS (Transcranial Magnetic Stimulation)	Neurophysiologic assessment of the excitability/integrity of the corticospinal pathway. Change in excitability is a measure of neural plasticity.	Motor threshold Motor evoked potential (MEP) and measurement of its properties: amplitude, latency, silent period, recruitment curve. Changes in these properties can measure neural plasticity
fMRI (Functional Magnetic Resonance Imaging)	Neurophysiologic assessment of blood flow within the brain during a functional task used to create brain maps of active brain regions.	Brain maps display the active brain areas during a specific task, when repeated after a physiotherapy intervention change in the areas of activity are a measurement of neural plasticity.

Table 32- The assessments that are completed at the baseline session of the FAST INdICATE trial and are repeated at the 6 week, and 6 month follow up sessions. The ARAT and WFMT assess upper limb motor control, the EQ-5D assesses health outcomes, and TMS and fMRI assess neural plasticity. References: (Schaechter, 2004, Wolf et al., 2001, Lang et al., 2006)

5.2.4 **Equipment**

The equipment used for TMS was identical to the equipment for the previous TMS study Chapter 4). Single pulse TMS was delivered using a Magstim 200 2 (Magstim Company Ltd, Carmarthenshire, UK) stimulator with a figure-of-eight coil 90 mm in diameter. The EMG/MEP data was collected from the biceps brachii and extensor carpi radialis using pre-prepared Ag-CL ConMed Cleartrace ECG round electrodes that were 20 mm in diameter (ConMed Patient Care, Utica NY, USA), and from the abductor pollicis brevis using Nicolet cup electrodes (CareFusion Nicolet P.O. Box 44994, Madison, WI, 53744-4994) with conducting gel/electrode cream (Grass EC2 electrode cream, Grass Products, Natus Neurology Middleton WI, USA). The EMG signals were pre-amplified and sampled using a Digitmier Ltd (Digitimer Ltd, Hertfordshire, UK) pre-amplifier, the CED (Cambridge Electronic Design) Micro 1401 (Cambridge Electronic Design Limited, Cambridge, UK), and the Neurolog System (Digitimer Ltd, Hertfordshire, UK). Please refer to section 0 Figure 18 page 120 for pictures of the equipment.

Muscles of investigation

The muscles of investigation were the biceps brachii, extensor carpi radialis (ECR), and abductor pollicis brevis (APB) of both the less affected and more-affected limbs. These muscles were selected because they are vital for successful reach to grasp and completion of ADL's. The biceps transports the arm in space, the ECR stabilises and extends the wrist enabling finger dexterity, and the APB abducts the thumb to allow for grasp and object manipulation (Shumway-Cook and Woollacott, 2007, Ngomo et al., 2012). These muscles are often paretic after a stroke and the target of many upper limb therapies (Donaldson et al., 2009, Wolf et al., 2006). The muscles investigated in the FAST INdICATE trial were the bilateral biceps and ECR. It is known that the different upper limb muscles have different corticospinal projections (Chen, 2000), respond differently to TMS (Martin et al., 2006), and have varying reliability of motor map area and slope of the recruitment curve (Carson et al., 2013, Malcolm et al., 2006). Therefore, due to the contribution of all muscles to functional use of the upper limb, different corticospinal projections, and response to stimulation the addition of the APB was included to investigate test-retest reliability of a muscle of the upper arm, forearm and hand.

5.2.5 **Procedures**

The procedures of the session can be found in Figure 45. Briefly, the procedures were reviewed, informed consent obtained, and then participants completed an identical TMS session to the baseline FAST INdICATE session.

Figure 45 - Procedures of Session

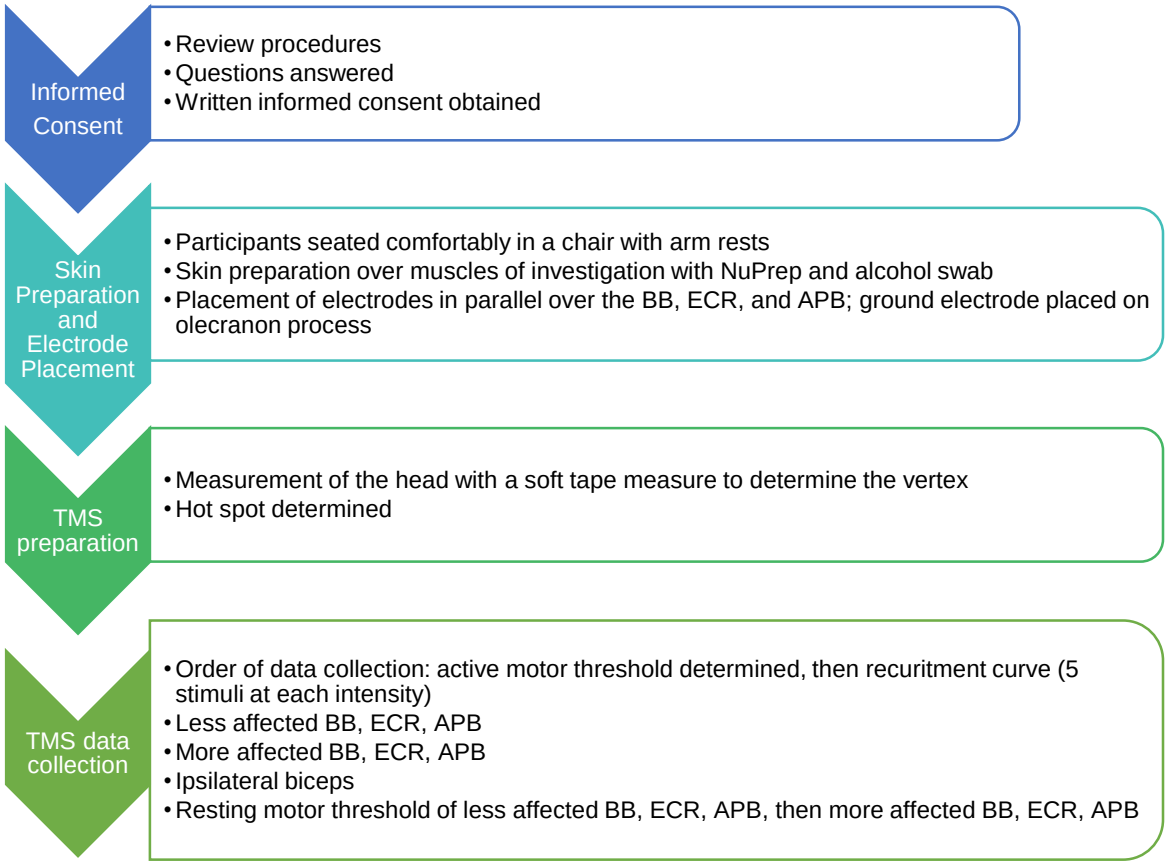


Figure 45- Procedures that occur during the TMS sessions

5.2.5.1 **Skin preparation and electrode placement**

The processes of skin preparation and electrode placement were identical to the procedures in section 4.2.7 page 123. Participants were seated comfortably in a chair with armrests. Participants were requested to make a muscle contraction if possible to locate the muscle belly. The skin over the muscles of investigation were abraded using Nuprep and alcohol swabs. Once the skin was dry, surface EMG electrodes were placed in parallel along the muscle fibres of the biceps, ECR and APB (Konrad, 2005); Figure 21 - Surface EMG Electrode Placement page 124 demonstrates electrode placement on each of the three muscles. A ground electrode was placed on the olecranon process. The electrodes were connected to the pre-amplifier with electrode leads.

5.2.5.2 **Data collection**

TMS data was collected in the same manner at both TMS sessions. The muscles were investigated in order starting with the non-paretic biceps, non-paretic ECR, paretic biceps, paretic ECR, paretic ipsilateral biceps, non-paretic APB, and finally the paretic APB. The process of data collection was identical for each muscle; and is described below for the paretic biceps. The process was similar to that of the data collection in the previous chapter.

- The EMG signals were pre-amplified at 10 Hz and 1 k gain, filtered at 10-50 Hz using the Neurolog system. Motor evoked potentials were collected using Signal 5.7 software and saved for offline analysis. EMG data was collected in 500 ms samples, 100 ms prior to the TMS stimulus and 400 ms after the TMS stimulus.
- The participants head was measured using a soft tape measure to determine the general area of the motor cortex, the vertex, and marked with permanent marker on the scalp Figure 22 - Measurement of the Head for Locating the page 125.
- Single-pulse TMS was delivered to the motor cortex contralateral to the muscles of interest. The TMS coil was placed tangentially to the scalp over the area of the motor cortex and vertex; with the handle pointing backwards to obtain a posterior-anterior current flow into the motor cortex (Koski et al., 2007a, Wassermann, 2002); Figure 25 - Coil Position during TMS Data Collection page 128.
- Participants maintained a slight biceps contraction as demonstrated in Figure 46. Assistance and cues (verbal/manual) were provided if participants needed assistance to maintain a muscle contraction. During active contraction there is a decrease in variability in the MEP caused by random fluctuations (Kiers et al., 1993), and maintaining a muscle contraction gives the participants a focus which may standardize the level of alertness during testing (Koski et al., 2007a).

Figure 46 - Slight Muscle Contraction

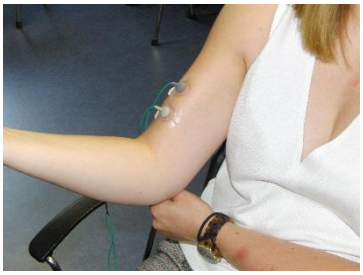


Figure 46A. Slight biceps contraction during TMS data collection (with EMG leads).

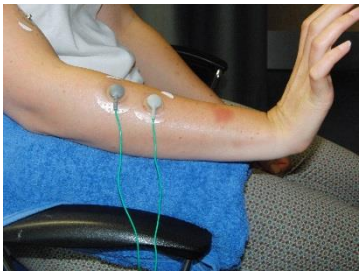


Figure 46B. Slight ECR contraction during TMS data collection (with EMG leads).

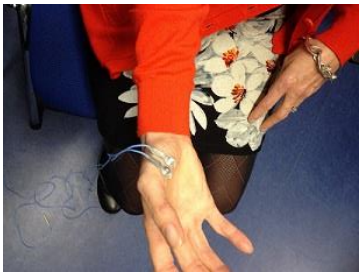


Figure 46C. Slight APB contraction during TMS data Collection (with EMG leads)

Figure 46 - Slight muscle contraction maintained during determination of the active motor threshold and data collection of the recruitment curve. Figure A is the biceps muscle, figure B the ECR, and figure C the APB. TMS=transcranial magnetic stimulation, EMG=electromyography, ECR=extensor carpi radialis muscle, APB= abductor pollicis brevis muscle

- During slight contraction the hot spot for the biceps was determined. The hot spot is the coil location on the scalp that the largest and most consistent MEP's are obtained from the muscle of interest (Carroll et al., 2001). Once the hot spot was determined it was marked on the scalp with a semi- permanent marker. All data related to the biceps brachii of the less-affected limb was collected from this point.
- The active motor threshold was then determined. The stimulator output was initially placed at a suprathreshold level and was decreased in 5% increments, then when closer to the threshold stimulator output was decreased in 1-2% increments until half of the successive trials produced an MEP > 200 µv (Koski et al., 2007a, Liu and Au-Yeung, 2014, Rossini and Rossi, 2007).
- Once the active motor threshold was determined a recruitment curve was obtained during a slight muscle contraction. Stimulation intensities included 100%, 110%, 120%, and 130% of active motor threshold; five TMS pulses were delivered at each intensity (Massie and Malcolm, 2013). Rest breaks were given as needed. Obtaining the recruitment curve during active conditions allows the motor threshold to be lower (lower stimulator output) enabling a greater percentage of the recruitment curve to be obtained because stroke survivors typically demonstrate higher motor thresholds (Massie and Malcolm, 2013, Koski

et al., 2007a). The process of determining the active motor threshold and obtaining a recruitment curve was repeated for all muscles.

- Next, the resting motor threshold was determined in the same manner as the active motor threshold. The resting motor threshold was the stimulator output in which half of successive trials elicited a MEP amplitude of > 50 μv (Rossini and Rossi, 2007, Ngomo et al., 2012).
- At the conclusion of active conditions and determining the resting motor threshold ipsilateral biceps responses were collected. TMS pulses were delivered over the hot spot for the less involved biceps while a slight biceps contraction was maintained; EMG responses were recorded from the more-affected biceps. TMS pulses were delivered at 120%, 140% and 160% of the active motor threshold of the less-affected biceps; five TMS pulses were given at each intensity.
- At the conclusion of the TMS session the electrodes were removed and the skin was cleansed.

Figure 47 - Processes during TMS Data Collection

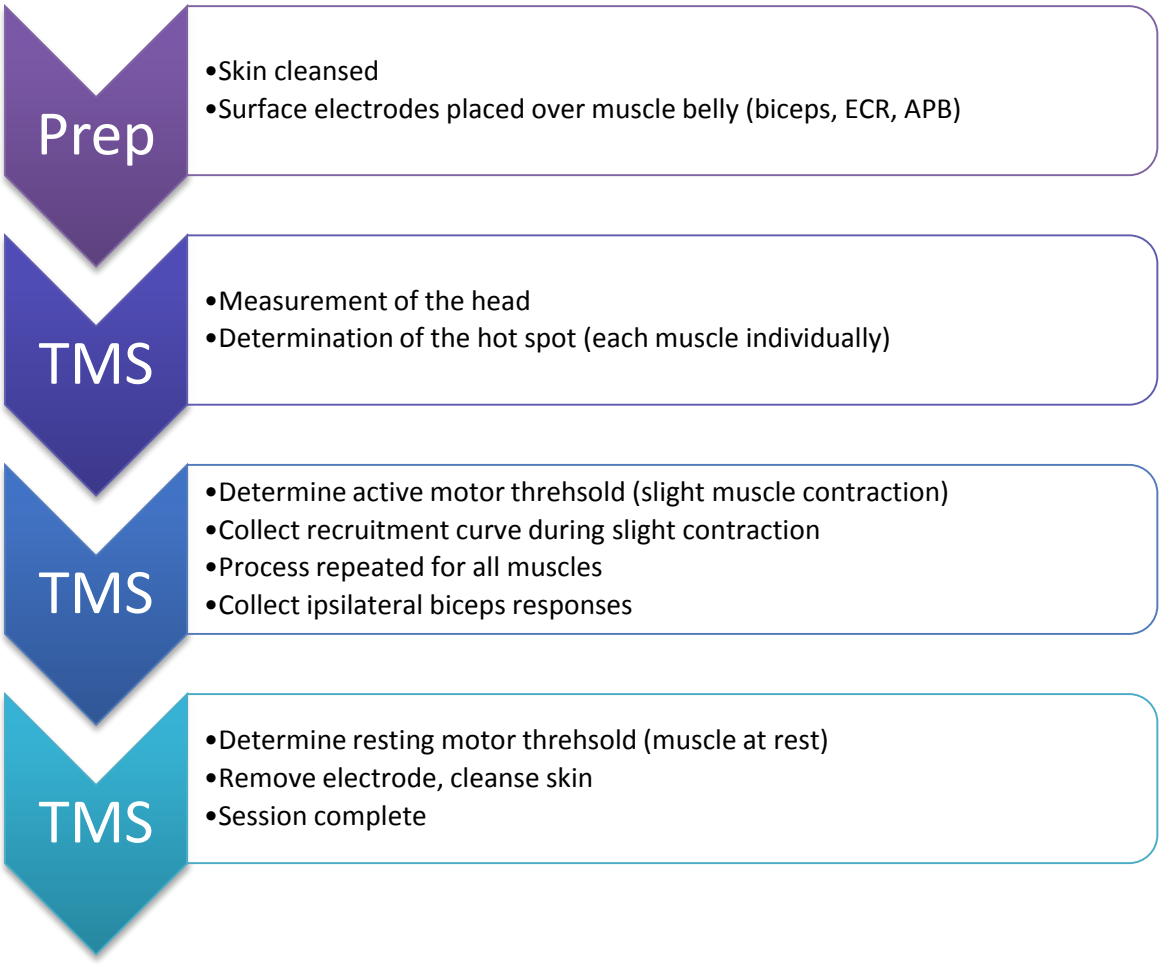


Figure 47 - Describes the processes completed during TMS data collection. The processes were identical at each session. The muscles were investigated in order starting with the non-paretic biceps, non-paretic ECR, paretic biceps, paretic ECR, ipsilateral biceps, non-paretic APB, and paretic APB.

5.2.6 **Data processing**

Signal Software was used to process the MEP amplitude, MEP latency, and the silent period; the recruitment curve was processed in Stata 12.1 software. The researcher visually assessed each MEP frame for appropriateness for analysis; taking into consideration presence of an MEP, quality of EMG/MEP, and presence of electrical noise. Trials without an MEP or with electrical noise were not analysed. The frames that were appropriate for analysis were “tagged” in signal. The processing of the MEP elements was identical to the processes used in the previous chapter ’Reliability of TMS measures of corticospinal excitability across the lifespan’. Briefly, the motor threshold was determined as the percentage of stimulator output needed to obtain an MEP in half of successive trial of at least 50 mV or 200mV for the resting and active motor thresholds respectively. The MEP amplitude was determined using a pre-written script in Signal

software (5.7) to measure the peak-to-peak amplitude in millivolts. The MEP max was the largest MEP amplitude (produced by the script) for the muscle of interest that was assessed by the researcher (MEP amplitude output from Signal). The silent period and MEP latency were assessed visually. The MEP latency was the time from stimulus to the first deflection of the MEP in milliseconds. The silent period was the time from MEP onset to return of EMG measured in milliseconds. The recruitment curve was plotted as the stimulator intensity again the MEP amplitude in Stata 12.1 software. For complete details of the data processing please refer to section 4.2.8 page 130.

5.2.7 **Statistical analysis**

The test-retest reliability was determined by comparing the findings from session one (baseline FAST INdICATE TMS) to the findings of session two (additional TMS session). Statistical analysis of the test-retest reliability was identical to the statistical analysis in Chapter 4. The test-retest reliability was robustly determined using the combination of the ICC model [2, 1] and Bland-Altman's 95% LOA (Bland and Altman, 1986b, Portney and Watkins, 2009, de Vet et al., 2006). The ICC assesses the agreement between measures from session one to session two; an ICC closer to one indicates better agreement. The ICC will be interpreted such that an ICC > 0.70 is acceptable reliability (Portney and Watkins, 2009), and interpreted with reference to the 95% CI. The lower end of the 95% CI was used to determine the test-retest reliability. The Bland-Altman plots assessed if there is error in agreement in the measurement from session one to session two as well as the variance between sessions (Bland and Altman, 1986b). For a more detailed description of statistical analysis please refer to section 4.2.9 page 133.

The ICC and LOA will be determined individually for each muscle of the paretic and non-paretic limbs.

Statistical analysis was completed using STATA SE version 12.1 software.

5.3 Results

5.3.1 Participants

Participants were recruited to participate in this study from the FAST INdICATE trial starting in February 2014 and ending in May 2015 Figure 48. During the time period of recruitment 41 individuals participated in FAST INdICATE baseline TMS. The 41 participants who completed baseline FAST INdICATE TMS were invited to participate in an additional session of TMS to investigate the test-retest reliability. Of the 41 individuals invited to participate 34 agreed to take part. Data was collected on 28 participants during a second TMS session. Reasons for not completing the second session are in Figure 48; briefly there were medical reasons or there were unforeseen circumstances preventing return to the second session. This study aimed to recruit 51 participants and recruited twenty-eight, however, 68% of the individuals invited to take part completed the second TMS session.

The mean age and SD of participants was 74±11 years, 15 men and 13 women. The mean time since stroke to the first TMS session was 38.6±19.8 days after stroke.

5.3.2 Trials analysed

There were 9.7% of trials that were not analysed because a MEP was not present or there was electrical noise preventing processing and analysis.

Figure 48 - Recruitment

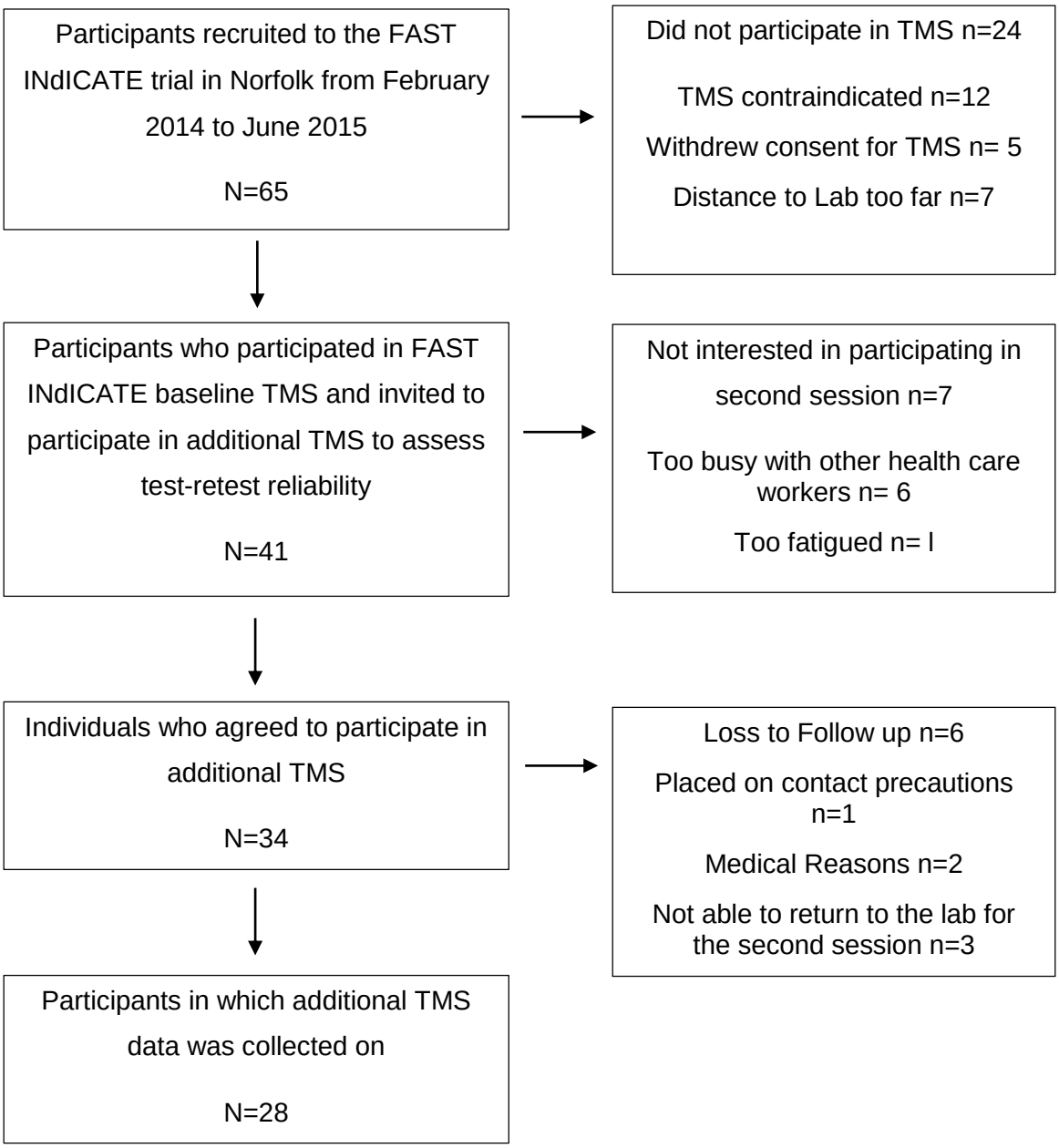


Figure 48 - Flow diagram of participants from the FAST INdICATE trial who were eligible to participate in TMS, invited to participate in the additional TMS session, and the participants who participated in the additional TMS session. The reasons for not participating in the additional TMS session are provided in the box on the right.

5.3.3 **Reliability of TMS measures**

Descriptive statistics for the MEP elements are in Table 33 to Table 35. Table 33 describes the mean and standard deviation of the motor threshold, MEP latency, silent period and slope of the recruitment curve from session one and session two. Table 34 and Table 35 demonstrate the mean and standard deviation of the average MEP amplitude and Max MEP amplitude respectively. Data were roughly normally distributed, example histograms are in Figure 49 A and B demonstrating the active motor threshold of the non-paretic and paretic ECR.

Table 33 Descriptive Statistics of the MEP elements in stroke survivors

Muscle	Limb assessed	AMT Session 1	AMT Session 2	RMT Session 1	RMT Session 2	MEP latency 130% AMT Session 1	MEP latency 130% AMT Session 2	Silent Period session 1	Silent Period Session 2	Recruitment Curve Slope Session 1	Recruitment Curve Slope Session 2
Biceps	Non-paretic	52±7	53±8	69±11	69±11	13.70±2.33	13.48±2.22	117.83±45.79	132.98±44.18	0.12±0.05	0.28±0.56
	Paretic	62±10	64±9	76±15	80±9	14.75±3.00	13.86±2.69	134.67±36.71	142.82±34.10		
ECR	Non-Paretic	40±5	41±6	53±11	53±10	16.59±1.80	17.13±4.60	112.39±36.81	127.81±41.12	0.20±0.12	0.047±0.17
	Paretic	54±13	57±12	66±14	72±12	18.87±5.62	18.53±1.89	154.21±41.08	160.72±40.50	0.06±0.05	0.06±0.05
APB	Non-paretic	42±6	43±7	50±11	50±15	23.58±2.55	23.01±2.04	151.58±51.20	152.62±37.72	0.10±0.07	0.12±0.07
	Paretic	53±15	58± 14	59±9	65±10	24.53±2.03	24.22±1.92	156.68±52.03	161.75±40.96	0.20±0.13	0.58±0.60

Table 33 Describes the mean and standard deviation of the MEP elements AMT, RMT, MEP latency, silent period and the slope of the recruitment curve for both session one and session two. AMT=active motor threshold, RMT= resting motor threshold, MEP =motor evoked potential, ECR=extensor carpi radialis, APB= abductor pollicis brevis

Table 34 Descriptive Statistics for the average MEP amplitude in stroke survivors

Muscle	Limb Assessed	% AMT	Average MEP Amplitude Session 1	Average MEP Amplitude Session 2
Biceps	Non-Paretic	100	0.72±0.48	0.53±0.27
		110	0.89±0.62	0.64±0.35
		120	1.06±0.80	0.81±0.48
		130	1.26±0.95	0.94±0.66
	Paretic	100	0.47±0.40	0.44±2.24
		110	0.76±1.34	0.48±0.27
		120	0.83±1.10	0.56±0.29
		130	1.08±1.72	0.63±0.37
ECR	Non-Paretic	100	1.52±0.91	1.92±1.46
		110	1.64±0.88	2.31±1.62
		120	2.01±1.01	2.72±1.67
		130	2.19±0.84	2.82±1.71
	Paretic	100	0.80±0.56	0.86±0.48
		110	0.92±0.65	0.99±0.67
		120	1.08±0.66	1.12±0.67
		130	1.25±0.73	1.25±0.67
APB	Non-Paretic	100	1.57±1.08	1.60±1.25
		110	1.80±1.25	2.22±1.28
		120	2.41±1.43	2.50±1.67
		130	2.65±1.63	2.75±1.65
	Paretic	100	1.11±0.78	1.36±1.79
		110	1.66±1.53	1.67±1.20
		120	1.84±1.91	1.80±2.01
		130	2.42±2.25	2.47±2.25

Table 34 Mean and standard deviation of the average MEP amplitude at 100%, 110%, 120% and 130% of AMT during slight muscle contraction. AMT=active motor threshold, MEP=motor evoked potential, ECR= extensor carpi radialis, APB=abductor pollicis brevis

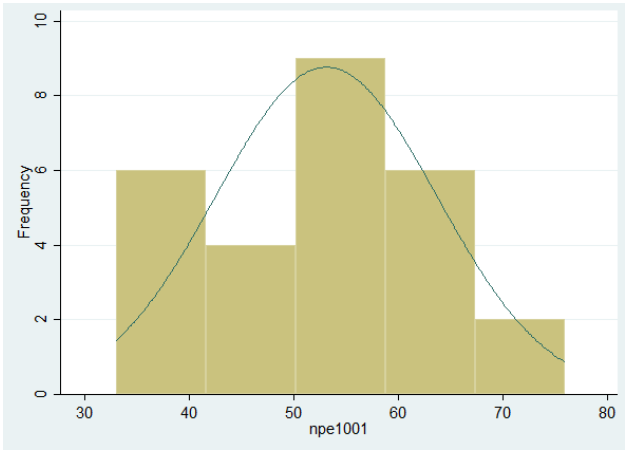
Table 35 Descriptive Statistics of the MEP Max Amplitude in stroke survivors

Muscle	Limb Assessed	MEP Max Amplitude Session 1	MEP Max Amplitude Session 2
Biceps	Non-Paretic	1.83±1.14	1.26±0.79
	Paretic	1.23±1.75	0.85±0.43
ECR	Non-Paretic	3.10±1.35	3.94±2.30
	Paretic	1.60±1.07	1.79±1.00
APB	Non-Paretic	3.60±1.90	3.62±1.89
	Paretic	2.99±2.27	3.27±4.14

Table 35 Describes the mean and standard deviation of MEP max of the biceps, ECR and APB of both the paretic and non-paretic limbs. ECR=extensor carpi radialis, APB=abductor pollicis brevis

Figure 49 Histogram of Data Distribution

A. Active motor threshold non-paretic ECR



B. Active motor Threshold paretic ECR

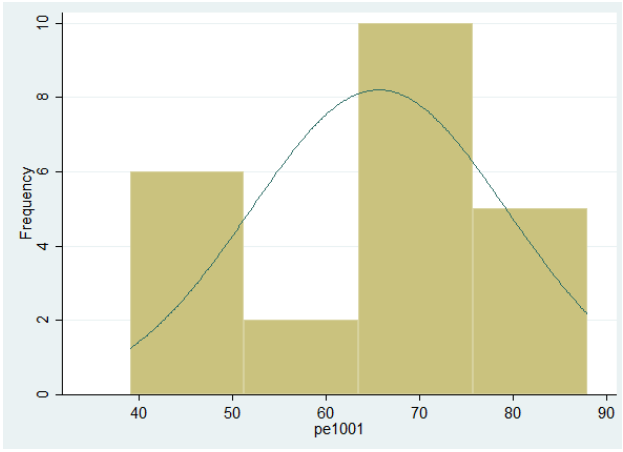


Figure 49 Histogram of data distribution of the active motor threshold of the paretic and non-paretic ECR demonstrating roughly normally distributed data

5.3.3.1 **Active Motor Threshold (AMT)**

The active motor threshold was able to be determined on non-paretic limb of all participants excluding the APB in one participant due to electrical noise. The motor threshold was not able to be determined for all participants paretic limb; the threshold was determined for the biceps 27/28, ECR 27/28, and APB 24/27 participant's paretic limb.

The ICC values and 95% LOA for the AMT of the bilateral biceps brachii, extensor carpi radialis, and abductor pollicis brevis are in Table 36; example Bland-Altman plots are in Figure 50 and in Appendix 21 for all muscles. The ICC estimated values for the active motor threshold range from ICC=0.586 (0.277 to 0.785) of the non-paretic biceps to ICC=0.837 (0.655 to 0.926) for the paretic APB. The lower end of the confidence interval falls within the range of poor reliability for the biceps and non-paretic APB. The 95% confidence interval and 95% LOA are wide indicating variability and imprecision in the results.

The Bland-Altman plots demonstrate random error in agreement between tests for both paretic and non-paretic muscles.

Table 36 - Reliability ICC and Limits of Agreement for the Active Motor Threshold

Muscle	Participants	ICC (95% CI)	95% LOA	Reliability Category
Non-Paretic Biceps	N=28	0.586 (0.277, 0.785)	-14.166 to 12.880	Poor
Paretic Biceps	N=27	0.602, (0.303, 0.795)	-19.259 to 14.815	Poor
Non-Paretic ECR	N=28	0.749, (0.529, 0.875)	-8.350 to 7.136	Moderate
Paretic ECR	N=27	0.826, (0.631, 0.922)	-16.668 to 11.608	Moderate
Non-Paretic APB	N=27	0.633, (0.346, 0.813)	-12.585 to 9.945	Poor
Paretic APB	N=24	0.837, (0.655, 0.926)	-18.440 to 12.531	Moderate

Table 36 - Reliability ICC and Limits of Agreement for the Active Motor Threshold assessed during slight muscle contraction of the paretic and non-paretic biceps, ECR, and APB. Reliability was assessed using the ICC model [2, 1], acceptable reliability is an ICC >0.70 (determined by the lower end of the confidence interval), and Bland-Altman's 95% LOA. In instances where the n < 28 the participants not included in the analysis were ones in which researcher was unable to determine a motor threshold within that muscle with the stimulator output up to 100% or as high as the participant could tolerate. ICC=intraclass correlation coefficient, LOA=limits of agreement, ECR=extensor carpi radialis muscle, APB=abductor pollicis brevis muscle

Figure 50- Bland-Altman Plots of the Active Motor Threshold

A.

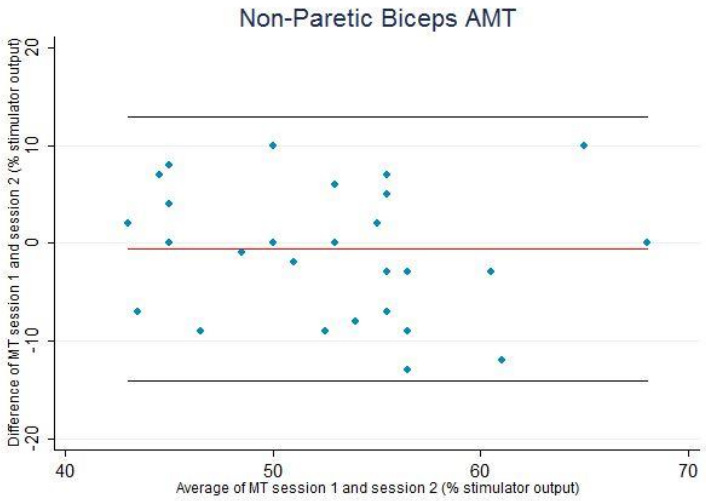


Figure 50 A Bland-Altman Plot of the AMT of the non-paretic Biceps muscle n=28

B.

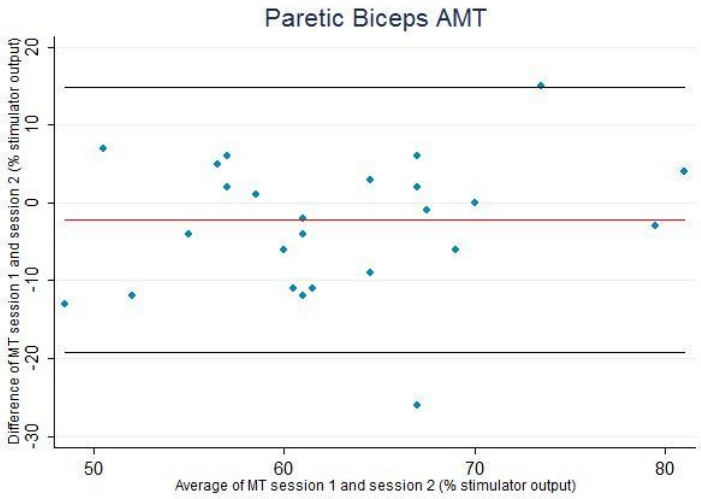


Figure 50 B Bland-Altman plot of the AMT of the paretic biceps Muscle, n=27

Figure 50 A & B - Bland-Altman plots of the AMT of the A) non-Paretic biceps muscle and B) the paretic biceps muscles. The x-axis represents the average MT of session one and session two, the y-axis represents the difference in MT of session one minus session two, the red line is the mean difference between sessions. Plots A and B represent random error in agreement between testing sessions. AMT=active motor threshold, MT=motor threshold

5.3.3.2 **Resting Motor Threshold**

The resting motor threshold was able to be determined on the non-paretic limb for all participants, with the exception of one participant's non-paretic APB due to electrical noise. The resting motor threshold was determined for the paretic biceps in 22/28 participants, ECR in 25/28 participants and the APB in 23/27 participants.

The reliability ICC and LOA of resting motor threshold for individual muscles can be found in Table 37, and example Bland-Altman plots are in Figure 51, the Bland-Altman plots for all muscles are in Appendix 21. The reliability is variable ranging from an ICC=0.418 (0.064 to 0.680) for the non-paretic biceps to ICC =0.806 (0.623 to 0.906) for the non-paretic extensor carpi radialis. The lower end of the confidence interval falls within the range of poor reliability with the exception of the non-paretic ECR and paretic APB. Furthermore, the 95% CI and 95% LOA are wide indicating variability and imprecision in the measurement.

The Bland-Altman plots demonstrate random error in agreement between tests for both paretic and non-paretic muscles, as well as outliers beyond the 95% LOA for all plots.

Table 37 - Reliability ICC and LOA of Resting Motor Threshold

Muscle	Participants	ICC	95 % LOA	Reliability Category
Non-paretic Biceps	N=28	0.418, (0.064,0.680)	-20.043 to 20.350	Poor
Paretic Biceps	N=22	0.627, (0.300, 0.824)	-27.267 to 19.933	Poor
Non-paretic ECR	N=28	0.806, (0.623, 0.906)	-14.367 to 14.219	Moderate
Paretic ECR	N=25	0.695, (0.422, 0.853)	-31.773 to 19.686	Poor
Non-Paretic APB	N=27	0.679, (0.402, 0.842)	-11.239 to 8.656	Poor
Paretic APB	N=23	0.765, (0.527, 0.892)	-25.369 to 15.035	Moderate

Table 37 - Reliability ICC and LOA of Resting Motor Threshold. The reliability of the resting motor threshold of the paretic and non-paretic biceps, ECR, and APB muscles. Reliability was assessed using the ICC model [2, 1] and Bland-Altman's 95% LOA. An ICC > 0.7 is acceptable reliability, was determined by the lower end of the confidence interval. In instances where the n < 28 the participants not included in the analysis were ones in which researcher was unable to determine a motor threshold within that muscle with the stimulator output up to 100% or as high as the participant could tolerate. ICC=intraclass correlation coefficient, LOA=limits of agreement, ECR=extensor carpi radialis muscle, APB=abductor pollicis brevis muscle

Figure 51 - Bland-Altman Plots of the Resting Motor Threshold

A.

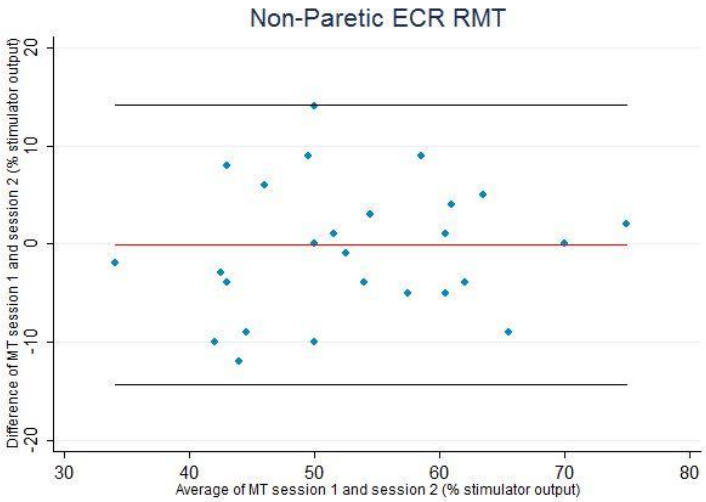


Figure 51A. Bland-Altman plot of the RMT of the Non-paretic ECR muscle, n=28

B.

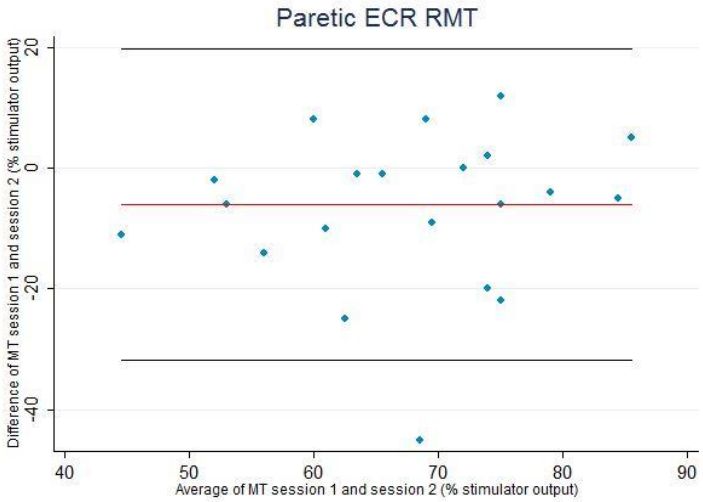


Figure 51B. Bland-Altman plot of the RMT of the paretic ECR muscle, n=25

Figure 51A & B - Bland-Altman plots of the RMT of the A) non-paretic ECR muscle and B) the paretic ECRs muscles. The x-axis represents the average MT of session one and session two, the y-axis represents the difference in MT of session one minus session two, the red line is the mean difference between sessions. Plots A and B represent random error in agreement between testing sessions. MT=motor threshold, RMT=resting motor threshold, ECR=extensor carpi radilias

5.3.3.3 **MEP amplitude**

The reliability of MEP amplitude for each individual muscle is in Table 38. The reliability is poor with the exception of the APB in whit the lower end of the confidence interval is within the range of moderate reliability ICC= 0.860 (0.699, 0.938) for the non-paretic APB. The 95 CI and 95% LOA are wide indicating variability and imprecision in the measurement.

Example Bland-Altman plots for the biceps are in Figure 52 - Bland-Altman Plots of Average MEP Amplitude and all plots are in Appendix 22. The Bland-Altman plots for biceps appear to have a greater proportion of differences between sessions that are below the mean difference line, indicating larger MEP amplitude on the second session. Additionally there appears to be a possible linear association such that the larger the MEP amplitude the greater the difference in amplitude between sessions for the paretic muscles. The Bland-Altman plots for the non-paretic ECR and APB demonstrate random error.

Table 38 - Reliability, ICC and LOA for the Average MEP Amplitude 100% to 130% AMT

Muscle	% of MT	ICC (95% CI)	95% Lower to Upper LOA	Reliability Category
NP Biceps n=28	100	0.493, (0.153, 0.729)	-0.564 to 0.937	Poor
N=28	110	0.553, (0.191, 0.774)	-0.618 to 1.144	Poor
N=28	120	0.369, (0.025, 0.642)	-1.204 to 1.708	Poor
N=28	130	0.300, (0, 0.593)	-1.582 to 2.236	Poor
P Biceps n=27	100	0.345, (0, 0.639)	-0.718 to 0.787	Poor
N=27	110	0.253, (0, 0.569)	-2.067 to 2.680	Poor
N=27	120	0.248, (0, 0.564)	-1.161 to 2.186	Poor
N=23	130	0.129, (0, 0.498)	-2.791 to 3.928	Poor
NP ECR n=28	100	0.470, (0.139, 0.711)	-2.865 to 2.067	Poor
N=28	110	0.439, (0.095, 0.692)	-3.312 to 1.978	Poor
N=28	120	0.361, (0.022, 0.635)	-3.468 to 2.218	Poor
N=28	130	0.411, (0.072, 0.670)	-3.468 to 2.218	Poor
P ECR n=23	100	0.398,(0.007, 0.682)	-1.217 to 1.076	Poor
N=25	110	0.543, (0.193, 0.770)	-1.335 to 1.195	Poor
N=23	120	0.461, (0.062, 0.731)	-1.450 to 1.323	Poor
N=22	130	0.441, (0.021, 0.725)	-1.500 to 1.451	Poor
NP APB n=27	100	0.775, (0.563, 0.891)	-1.541 to 1.582	Moderate
N=27	110	0.593, (0.203, 0.764)	-2.571 to 1.842	Poor
N=27	120	0.568, (0.291, 0.790)	-3.202 to 2.927	Poor
N=27	130	0.588, (0.273, 0.789)	-3.233 to 3.044	Poor
P APB n=24	100	0.306, (0, 0.627)	-3.511 to 2.998	Poor
N=24	110	0.723, (0.457, 0.870)	-2.713 to 2.463	Poor
N=21	120	0.860, (0.699, 0.938)	-2.140 to 1.952	Moderate
N=19	130	0.754, (0.461, 0.898)	-3.105 to 3.130	Poor

Table 38 - The test-retest reliability of the average MEP amplitude of the non-paretic and paretic biceps, ECR and APB at 100%, 110%, 120%, and 130% of AMT. The test-retest reliability was assessed using the ICC model [2,1] and associated 95% CI acceptable reliability is an ICC > 0.70, and the Bland-Altman 95% LOA. In instances where there are less than 28 participants included in the analysis the researcher was unable to determine a motor threshold with the stimulator up to 100%, or with increasing % of AMT the stimulator output was > 100% or the increasing stimulator output was uncomfortable thus not completed. MEP=motor evoked potential, ECR=extensor carpi radilalis muscle, APB=abductor pollicis brevis muscle, P=paretic muscle, NP=non-paretic muscle ICC=intraclass correlation coefficient, LOA=limits of agreement, MT=motor threshold

Figure 52 - Bland-Altman Plots of Average MEP Amplitude

A.

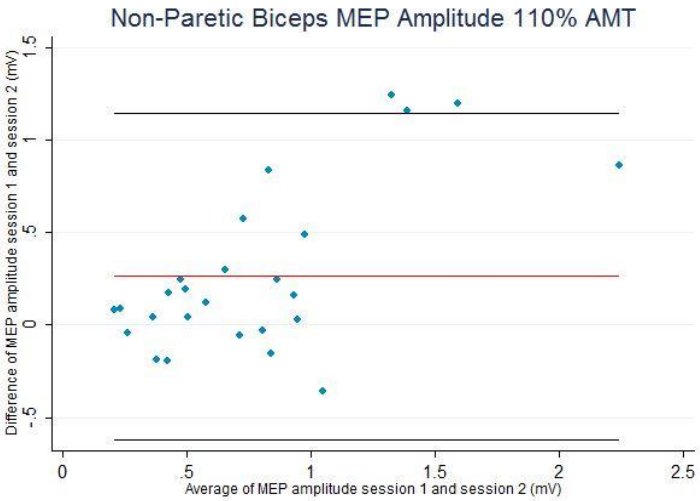


Figure 52A. Bland-Altman plot of the average MEP amplitude of the non- paretic biceps muscle at 110% AMT n=28

B.

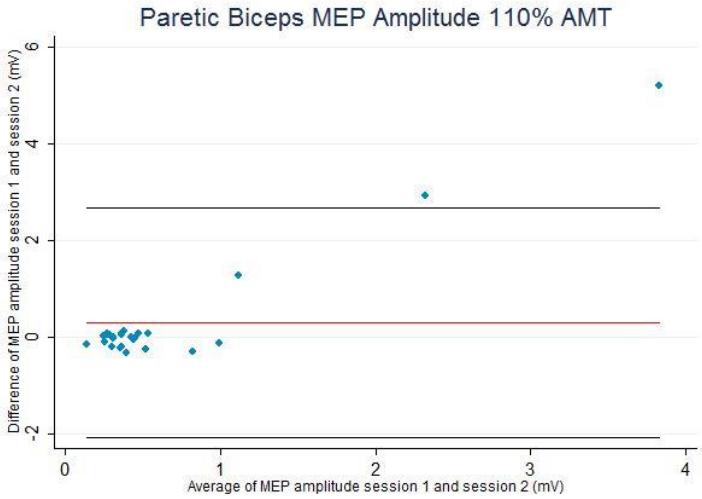


Figure 52 B. Bland-Altman plot of the average MEP amplitude Of the paretic biceps muscle at 110% AMT n=27

Figure 52 - Bland-Altman Plots of Average MEP Amplitude of the A non- paretic biceps muscle and B paretic biceps muscle assessed at 100% AMT. The x-axis represents the average MEP amplitude of session one and session two, the y-axis represents the difference in average MEP amplitude of session one minus session two, the red line is the mean difference in amplitude between session one and session two. Plot A demonstrates a potential association between MEP amplitude and difference between sessions. Plot B represents systematic error suggesting that the MEP amplitude of the second session was greater than the first session, and there is a potential linear association between MEP amplitude and agreement between sessions.

5.3.3.4 **Amplitude of MEP max**

The MEP max was the largest MEP amplitude collected for the muscle of interest. The reliability of the amplitude of MEP max for each individual muscle is in Table 39. Example Bland-Altman plots are in Figure 53 plots for all muscles are in Appendix 23. The reliability is poor for all muscles.

The Bland-Altman plots demonstrate random a potential association between increasing amplitude and a greater difference in amplitude between sessions. The plot for the paretic biceps demonstrates a greater number of differences below the mean difference line suggesting a larger amplitude at the second session.

Table 39 - Reliability of the Amplitude of MEP Max

Muscle	Participants	ICC (95% CI)	95% Limits of Agreement	Reliability Category
Non-Paretic Biceps	N=28	0.208 (0, 0.515)	-1.861 to 2.989	Poor
Paretic Biceps	N=27	0.232 (0, 0.553)	-2.774 to 3.535	Poor
Non-Paretic ECR	N=28	0.463 (0.127, 0.706)	-4.622 to 2.928	Poor
***Paretic ECR**	N=25	0.701 (0.435, 0.855)	-1.761 to 1.410	Poor
***Non-Paretic APB**	N=27	0.733 (0.451, 0.865)	-2.813 to 2.715	Poor
Paretic APB	N=24	0.198 (0, 555)	-9.008 to 8.104	Poor

Table 39 - The reliability of the maximum MEP amplitude during slight muscle contraction of paretic and non-paretic biceps, ECR, and APB. The test-retest reliability was assessed using the ICC model [2,1] and associated 95% CI acceptable reliability is an ICC >0.70, and the Bland-Altman 95% LOA. In instances where there are less than 28 participants included in the analysis the researcher was unable to determine an motor threshold with the stimulator up to 100%, or with increasing % of AMT the stimulator output was > 100% or the increasing stimulator output was uncomfortable thus not completed. MEP=motor evoked potential, ECR=extensor carpi radilalis muscle, APB=abductor pollicis brevis muscle, P=paretic muscle, NP=non-paretic muscle ICC=intraclass correlation coefficient, LOA=limits of agreement, MT=motor threshold, ECR= extensor carpi radialis, APB= abductor pollicis brevis

Figure 53- Bland-Altman Plot of MEP Max Amplitude

A.

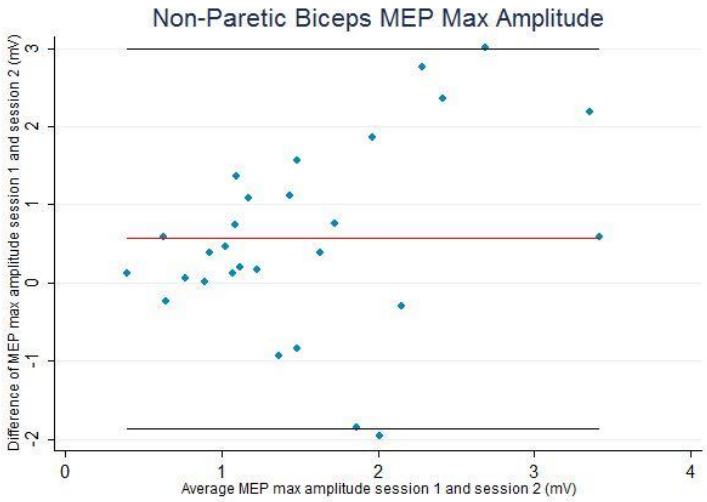


Figure 53 A- Bland-Altman plot of the non-paretic biceps MEP max amplitude n=28

B,

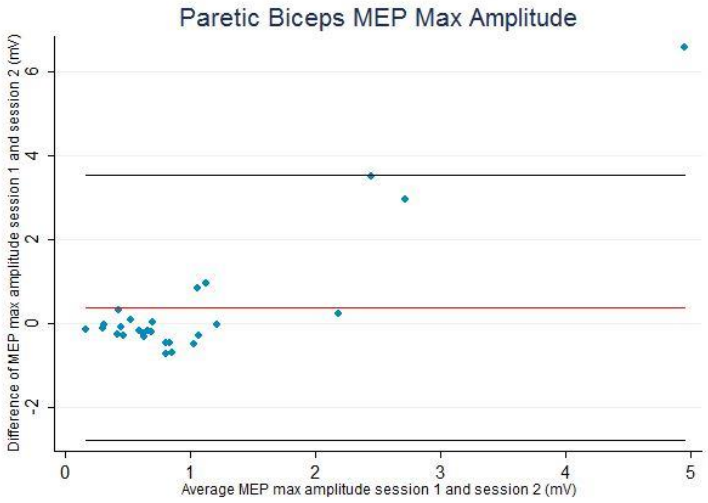


Figure 53 B Bland-Altman plot of the paretic biceps MEP max amplitude n=27

Figure 53 A, B- Bland-Altman plots of MEP max amplitude of the A) non-paretic biceps and B) paretic biceps. The x-axis represents the average MEP max amplitude of session one and session two, the y-axis represents the difference in average MEP max amplitude of session one minus session two, the red line is the mean difference in amplitude between sessions. Plot A demonstrates a potential association between MEP max amplitude and difference between sessions. Plot B demonstrates a great number of differences between sessions are below the mean difference (larger amplitude second session) and there is a potential association between MEP amplitude and agreement between sessions.

5.3.3.5 **Reliability of MEP latency**

The researcher visually assessed the MEP latency, another researcher assessed 10% of trials. The researchers were in agreement within 2 seconds on 84% of trials. The test-retest reliability of MEP latency at 120% and 130% of AMT is in Table 40 demonstrating reliability is variable. The lowest ICC value is for the paretic ECR at 130% of AMT ICC = 0.299, (0, 0.645), the highest ICC value is for the paretic biceps ICC=0.844 (0.685, 0.927). The lower end of the confidence interval falls within the poor range for most muscles excluding the non-paretic APB and the paretic biceps at 120% AMT. The 95% CI and 95% LOA are wide indicating variability and imprecision in measurement. The 95% LOA are wider when the latency is assessed at 130% AMT suggesting greater variability and imprecision in measurement 130% AMT compared to 120% AMT.

Example Bland-Altman plots are in Figure 54, plots for all muscles are in Appendix 24. The Bland-Altman plots of the latency assessed at 120% demonstrate random error in agreement between sessions.

The Bland-Altman plots of MEP latency of the non-paretic APB assessed at 130% AMT demonstrates systematic such that the latency was shorter the second session. The latency of the paretic ECR at 130% AMT demonstrates a trend towards the latency being longer the second session.

Table 40 - Reliability ICC and LOA of MEP Latency at 120% and 1305 AMT

Muscle	120% AMT ICC (95% CI)	95% LOA	Reliability Category	130% AMT ICC 95% CI	95% LOA	Reliability Category
Non-Paretic Biceps n=26	0.499, (0.170, 0.730)	-3.133 to 2.461	Poor	0.715, (0.463, 0.860)	-5.250 to 4.501	Poor
Paretic Biceps n=21	0.844 (0.685, 0.927)	-3.623 to 4.14	Moderate	0.658, (0.321, 0.846)	-6.871 to 7.225	Poor
Non-Paretic ECR n=26	0.494 (0.154, 0.729	-4.396 to 3.798	Poor	0.392, (0.030, 0.669)	-4.414 to 3.210	Poor
Paretic ECR n=21	0.539 (0.168, 0.775)	-7.104 to 6.345	Poor	0.299, (0, 0.645)	-10.396 to 11.505	Poor
Non-Paretic APB n=25	0.762 (0.526, 0.889)	--3.328 to 3.870	Moderate	0.668, (0.386, 0.838)	-22.960 to 19.548	Poor
Paretic APB n=22	0.451 (0.035, 0.730)	-5.442 to 5.785	Poor	0.774, (0.473, 0.912	-3.366 to 3.508	Poor

Table 40 - Test-retest reliability of MEP latency of the paretic and non-paretic biceps, ECR, and APB muscles assessed at 120% and 130% of AMT. The test-retest reliability was assessed using the ICC model [2,1] and associated 95% CI acceptable reliability is an ICC >0.70, and the Bland-Altman 95% LOA. In instances where there are less than 26 participants included in the analysis the researcher was unable to determine a motor threshold with the stimulator up to 100%, or with increasing % of MT the stimulator output was > 100% or the increasing stimulator output was uncomfortable thus not completed. ECR= extensor carpi radialis, APB= abductor pollicis brevis, AMT=active motor threshold, LOA=limits of agreement, ICC=intraclass correlation coefficient, MEP=motor evoked potential

Figure 54- Bland Altman Plots of MEP Latency

A.

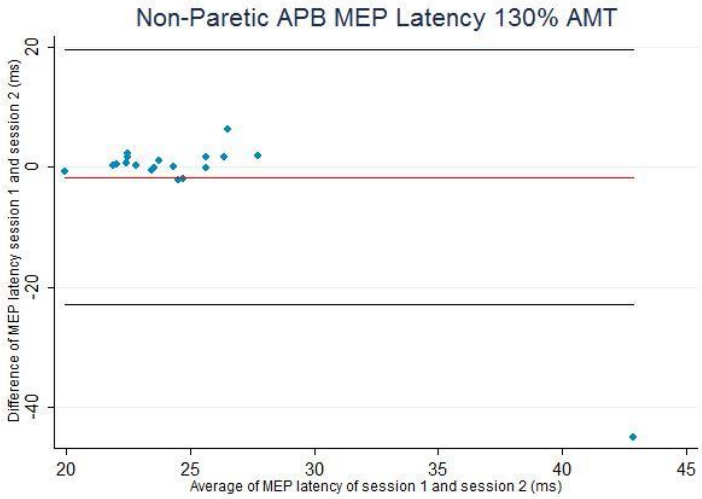


Figure 54 A. Bland-Altman plot of the MEP latency of the Non- paretic APB assessed at 130% of AMT n=25

B.

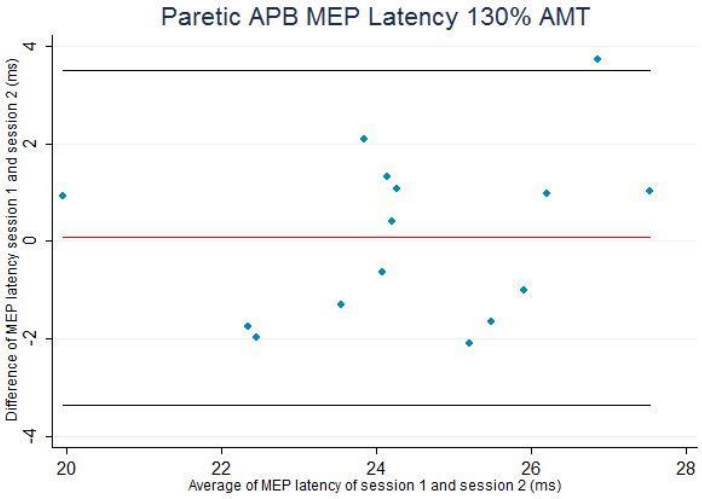


Figure 54 B. Bland-Altman plot of the MEP latency of the paretic APB assessed at 120% AMT n=22

Figure 54- Bland Altman Plots of MEP Latency of A the non-paretic APB assessed at 130% AMT and the paretic APB assessed at 120% AMT. The x-axis is the average latency of session one and session two, the y-axis is the difference in latency from session one minus session two, the red line is the mean difference between session one and session two. Plot A demonstrates systematic error such that the latency was shorter at the second session. Plot B demonstrates a potential linear association between latency duration and difference between sessions.

5.3.3.6 **Recruitment Curve**

The reliability of the slope of the recruitment curve is in Table 41, example Bland-Altman plots are in Figure 55, and plots for all muscles are in Appendix 26. Not all participants' data was able to be fitted with a sigmoidal function. The sigmoidal function was fitted for 9/28 participants for their non-paretic biceps, 1/27 for their paretic biceps, 2/28 for their non-paretic ECR, 4/24 for the paretic ECR, 8/27 for the non-paretic APB, and 6/22 for the paretic APB. The varied number of participants (denominator) is the number of participants in which an active threshold was able to be determined. Some participants did not demonstrate increasing MEP amplitude with increasing stimulus intensity non-paretic biceps 7/26, non-paretic ECR n=5/28, non-paretic APB 4/27, paretic biceps n=8/25, paretic ECR n=6/22, and paretic APB n=3/20). Previous studies have also reported that not all participants' data were able to be fitted to a sigmoidal function for example Schambra et al (2015) reported that 12.7% of chronic stroke survivors and 9.4% of sub-acute stroke survivors did not fit a sigmoidal function.

The reliability of the slope of the recruitment curve was poor for all muscles.

The Bland-Altman plot of the slope of the recruitment curve of the non-paretic APB demonstrates a lesser slope at the second session.

Table 41 - Reliability (ICC and LOA) of Slope of the Recruitment Curve

Muscle	Participants	ICC (95% CI)	95% LOA	Reliability Category
Non-Paretic Biceps	N=9	0.058, (0, 0.628)	-1.5117675 to 1.5126896	Poor
Paretic Biceps	N=1	Not completed	Not completed	Not completed
Non-Paretic ECR	N=2	0.194, (0, 0.998)	-3.2706015 to 1.6643126	Poor
Paretic ECR	N=4	0.780, (0, 0.985)	-.07392636 to .07112499	Poor
Non-Paretic APB	N=8	0.032, (0, 0.618)	-2.9913301 to 1.7774199	Poor
Paretic APB	N=6	0.598, (0, 0.476)	-2.1103892 to 1.7585417	Poor

Table 41 - Test-retest reliability of the slope of the recruitment curve of the paretic and non-paretic biceps, ECR and APB muscles. The test-retest reliability was assessed using the ICC model [2,1] and associated 95% CI, ICC >0.70 acceptable reliability is an ICC > 0.7, and the Bland-Altman 95% LOA. The reliability of the slope of the RC poor all muscles, and the 95% CI span negative reliability. Not all participants' data were able to be fitted with a sigmoidal function, the number of participants data that were able to be fitted is reported in the participant column. ECR= extensor carpi radialis, APB= abductor pollicis brevis, AMT=active motor threshold, LOA=limits of agreement, ICC=intraclass correlation coefficient, MEP=motor evoked potential

Figure 55 - Bland-Altman Plot of the Recruitment Curve

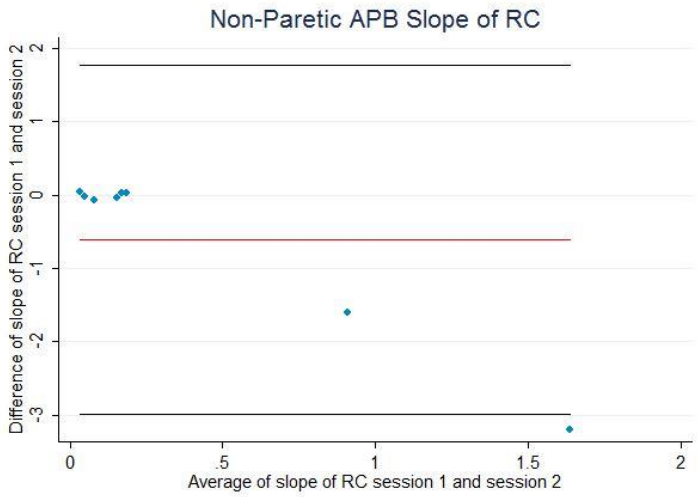


Figure 55 - Bland-Altman plot of the slope of the recruitment curve of the non-paretic APB muscle. The x-axis represents the average slope of the RC of session one and session two, the y-axis represents the difference in slope of the RC of session one minus session two, the red line is the mean difference between session one and session two. The plots represents a greater number of differences between sessions has a less steep slope at session two. n=8

5.3.3.7 **Silent Period**

The test-retest reliability of the silent period assessed at 130% of AMT is in

Table 42, example Bland-Altman plots are in

Figure 56, all plots are in Appendix 25. Not every participant demonstrated a clear silent period. The silent period of the non-paretic biceps was determined in 24/28 participants, the paretic biceps in 22/27, the non-paretic in ECR 24/28, paretic in ECR 22/23, non-paretic in APB: 22/27, and paretic in APB: 16/24 participants.

The test-retest reliability of the silent period is variable ranging from poor to good. The lower end of the confidence interval falls within the range of poor for all muscles with the exception of the paretic APB which falls within moderate reliability. The ICC ranges from an ICC= 0.165 (0, 0.500) for the non-paretic ECR to ICC= 0.866 (0.662, 0.951) for the paretic APB. The 95% CI and 95% LOA are wide for all muscles indicating variability and imprecision in the measurement.

The Bland-Altman plots of the paretic ECR and APB demonstrate a potential association between the length of the silent period and greater differences between sessions. The plots of the other muscles demonstrate random error in agreement between sessions.

Table 42 - Reliability ICC and LOA of the Silent Period Assessed during 130% AMT

Muscle	Participants	ICC (95% CI)	95% LOA	Reliability Category
Non-Paretic Biceps	N=24	0.536, (0.199, 0.760)	-91.006 to 78.159	Poor
Non-Paretic ECR	N=24	0.165, (0.500)	-96.228 to 78.796	Poor
Non-Paretic APB	N=26	0.656, (0.360, 0.834)	-88.526 to 84.572	Poor
Paretic Biceps	N=22	0.458, (0.043, 0.735)	-107.579 to 100.494	Poor
Paretic ECR	N=22	0.820, (0.619, 0.920)	-54.594 to 40.653	Moderate
Paretic APB	N=16	0.866, (0.662, 0.951)	-47.516 to 38.512	Moderate

Table 42 - ICC (95% CI) and 95% LOA of the silent period assessed during 130% AMT, with slight background muscle contraction of the paretic and non-paretic biceps, ECR and APB muscles. The test-retest reliability was assessed using the ICC model [2,1] and associated 95% CI, acceptable reliability is an ICC > 0.7 and the Bland-Altman 95% LOA. In instances where there are less than 28 participants included in the analysis the researcher was unable to determine an motor threshold with the stimulator up to 100%, or with increasing % of MT the stimulator output was > 100% or the increasing stimulator output was uncomfortable thus not completed. ECR= extensor carpi radialis, APB= abductor pollicis brevis, AMT=active motor threshold, LOA=limits of agreement, ICC=intraclass correlation coefficient, MEP=motor evoked potential

Figure 56-Bland-Altman Plot of the Silent Period

A.

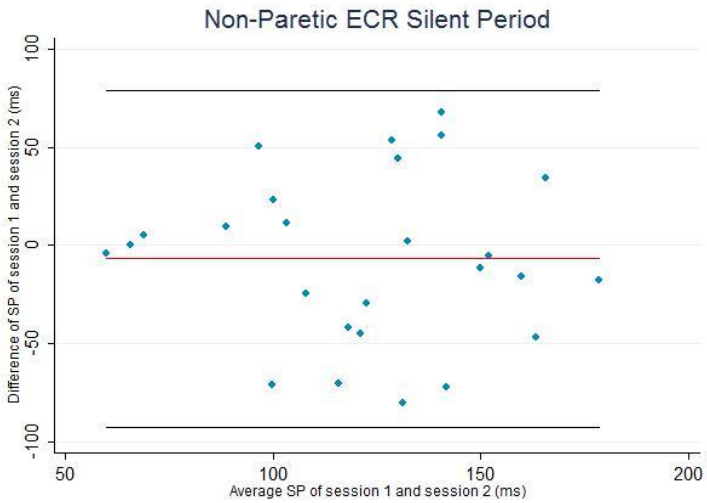


Figure 56 A Bland-Altman plot of the silent period of the non-paretic ECR n=26

B.

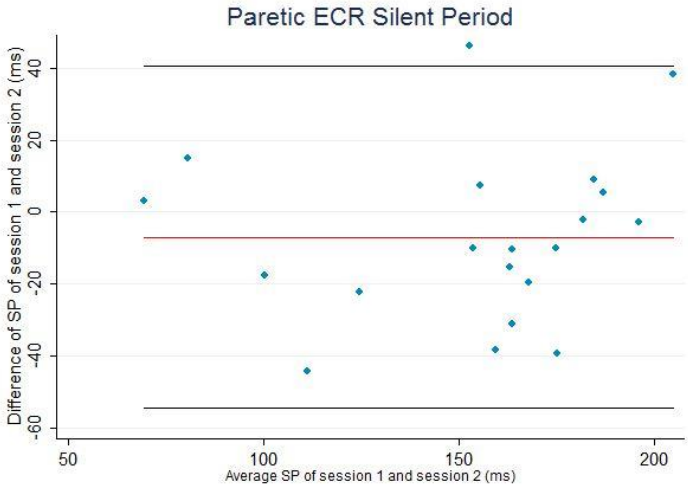


Figure 56- Bland-Altman plot of the silent period of the paretic ECR n=22

Figure 56 A, B Bland-Altman Plot of the silent period of the A) non-paretic ECR and B) paretic ECR assessed at 130% AMT. The x-axis represents the average SP of session one and session two, the y-axis represents the difference in SP of session one minus session two, the red line is the mean difference between sessions. Plot A demonstrates random error in agreement between sessions. Plot B demonstrates a potential association between SP duration and difference between sessions. AMT=active motor threshold, ECR=extensor carpi radialis, SP=silent period

5.4 Discussion

In summary the findings demonstrate that in this population of stroke survivors in the first three months after stroke the test-retest reliability of TMS measures of corticospinal excitability is variable; the lower end of the confidence interval was below acceptable reliability on most measures (ICC <0.70). The 95% confidence intervals and limits of agreement are wide further demonstrating imprecision in the measurement. The Bland-Altman plots demonstrate random error between tests for most measures, excluding the MEP amplitude in which there is a trend towards a greater difference between measures as MEP amplitude increases. This suggests there may be an association between measurement error and the magnitude of the measurement. These findings suggest that TMS may not be suitable to detect change in corticospinal pathway excitability in individual participants.

The excitability of the corticospinal pathway in this group of stroke survivors is comparable to some previously published data. The motor threshold for the APB (42±6 to 50±11 (% of stimulator output) non-paretic, and 53±15 for the non-paretic) was comparable to previous findings of the motor threshold of the FDI another thenar muscle in a group of sub-acute stroke survivors (51.15±12.65 for the paretic and 47.22±10.46 non-paretic) (Schambra et al., 2015). Alternatively, the motor threshold for the APB was lower than the FDI in other research of chronic and subacute stroke survivors (Brouwer and Schryburt-Brown, 2006). The MEP max amplitude is smaller in the present study for the non-paretic limb and larger for the paretic limb than earlier findings of the FDI (Koski et al., 2007b). Whereas, the average MEP amplitude of the paretic limb is larger than other studies of the FDI amplitude (Brouwer and Schryburt-Brown, 2006). The ABP latency was comparable to that of the FDI in a group of subacute stroke survivors, but the silent period was shorter in the present study (Brouwer and Schryburt-Brown, 2006). The present findings of the ECR RMT are higher than earlier investigations (MT=54-55 % of stimulator output) in stroke survivors one month after stroke, however the ECR

amplitude identified in this study was smaller than earlier research (Castel-Lacanal et al., 2009). There is limited research of corticospinal pathway excitability of the biceps muscle in stroke survivors. The differences found between the findings of this study and previous studies may be due to the rate of neural plasticity/spontaneous recovery (Cramer 2008), the different muscles assessed such as comparing the APB to the FDI as they receive different corticospinal pathway inputs (Martin et al., 2006) as well as the differing TMS methodology which will be discussed further in Chapter 6.

Comparing the values of corticospinal pathway excitability of the stroke survivors within this chapter to the neurologically intact stroke survivors in Chapter 4, in general the non-paretic limb is comparable to the neurologically intact adults while the paretic limb demonstrates less corticospinal pathway excitability. For example, the active and resting motor thresholds of the non-paretic limb are comparable to all three muscles of the neurologically intact adults, however the non-paretic limb demonstrates wider confidence intervals suggesting greater variability. The motor thresholds for the paretic limb are higher for all three muscles compared to the non-paretic limb and neurologically intact adults e.g. ECR AMT 57±12 paretic limb, 40±5 neurologically intact adults, 40±15 non-paretic limb. The MEP latency of the paretic limb was about 2 ms slower than the neurologically intact adults, whereas the latency of the non-paretic limb was similar to neurologically intact adults. The silent period was longer in both the paretic and non-paretic limbs compared to neurologically intact adults; the paretic limb demonstrated longer silent periods compared to the non-paretic limb. The silent period was between 6-60 ms longer in stroke survivors, for example the silent period of the paretic ECR was 154.21±41.08 paretic limb, 112.39±36.81 non-paretic limb, and 98.03±28.21 for the dominant limb of neurologically intact adults. The MEP amplitude of stroke survivors' non-paretic limb was comparable for the ECR and APB, however the biceps amplitude was smaller. The MEP amplitude of stroke survivors' paretic limb was smaller for all three muscles compared to neurologically intact adults e.g. biceps at 110% AMT 1.22 ±0.77 in neurologically intact adults, 0.48±0.27 for stroke survivors' paretic limb, and 0.64±0.35 for the non-paretic limb. These findings of changes in corticospinal pathway excitability in stroke survivors compared to neurologically intact adults is in line with earlier research (Cacchio et al., 2011, Brouwer and Schryburt-Brown, 2006, Schambra et al., 2015).

Overall, the distal muscles tend to demonstrate higher ICC values for motor threshold, MEP amplitude, and MEP max amplitude compared to the proximal biceps muscle. Previous research has demonstrated that distal muscles have a greater response to brain stimulation compared to proximal muscles (Martin et al., 2006); the greater response (of distal muscles) to stimulation may be a contributing factor to their reliability.

Additionally, the paretic muscles tended to demonstrate higher ICC values for the motor threshold, MEP max and silent period, whereas, the non-paretic muscles demonstrated higher ICC values for the average MEP amplitude however the differences were not significant. The higher ICC values in the paretic muscles demonstrating higher ICC has been demonstrated previously (Koski et al., 2007a). The difference in reliability suggests that specific TMS measures may be better used for the paretic and non-paretic upper limbs to measure corticospinal pathway excitability.

A challenge to the experimental set up was that some stroke survivors had difficulty maintaining a sufficient muscle contraction during data collection. The muscle contraction was monitored by the researcher though vision, palpation, and assessment of the 100 ms of EMG prior to TMS stimulus. In instances in which participants fatigued they were given rest breaks, or if there was too a strong muscle contraction, participants rested and then the slight contraction was re-demonstrated and explained. Varied or fluctuating strength of muscle contraction can influence MEP amplitude (Rösler et al., 2002) and thus could have influenced the reliability of the MEP elements.

An inclusion criteria of the FAST INdICATE trial was: “no obvious motor dyspraxia or communication deficits as assessed by the ability to imitate action with the non-paretic upper limb. The accuracy of imitation of observed activity will be assessed on the 3-point scale used by Decety: 2=correctly reproduced action, 1= incorrectly reproduced action, 0=not reproduced. Those scoring greater than or equal to 8/10 will be considered to have the ability to imitate and included in the trial” therefore individuals with severe dyspraxia or communication deficits were not included in the study. There were participants that exhibited neglect or decreased attention to the paretic side; those participants were given extra cues and assistance as needed. Additionally, participants had varying levels of alertness and fatigue on the two different days as well as throughout the session. There is evidence that attention and level of alertness can influence corticospinal pathway excitability (Abbruzzese et al., 1996, Darling et al., 2006, Kiers et al., 1993). The fluctuating muscle contraction, attention and fatigue may have influenced all MEP elements and the reliability of the MEP elements.

5.4.1 **Strengths of the Study**

This study was one of few studies to investigate the test-retest reliability of TMS measures in a group of sub-acute stroke survivors.

The strengths of the study include the investigation of test-retest reliability of multiple TMS measures such as active and resting motor threshold, MEP latency, silent period, MEP amplitude, MEP max amplitude, and the recruitment curve.

The present study investigated the test-retest reliability of TMS measures in three upper limb muscles the biceps, ECR and APB. Previous research has limited test-retest reliability investigations to mainly the hand muscles.

The present findings have expanded on previous research of the test-retest reliability measures by providing evidence of the reliability in a range of muscles and MEP elements in stroke survivors early after stroke.

The Bland-Altman plots demonstrate a possible association between magnitude of MEP amplitude and agreement between sessions. The larger the MEP amplitude the greater the difference in amplitude between sessions; this is in line with similar findings of the biceps MEP amplitude (Sankarasubramanian et al., 2015) warranting future investigation. Measurement of MEP amplitude at lower stimulation intensities or lower percentage of motor threshold would yield smaller amplitudes and may be beneficial to decrease variability and improve agreement in TMS measurement between sessions.

5.4.2 **Limitations**

The TMS data was collected during active muscle contraction however there was not a specific percentage of muscle contraction maintained. Participants were instructed to maintain a slight muscle contraction that was monitored by the researcher. It is possible there was variability in muscle contraction within and between sessions contributing to variability in MEP amplitude, latency, motor threshold, recruitment curve and subsequently the lower ICC values obtained.

The time interval between the two sessions may have been too long, resulting in spontaneous recovery and task-dependent neural plasticity being reflected in the TMS measurement. Therefore the interval between sessions may have contributed to lower ICC values and variability in the results.

The study was underpowered; there may not have been enough participants included in the analysis to have statistical power. A power calculation was completed prior to study initiation; based on the power calculation fifty-one participants needed to be recruited to the study; however 28 participants were recruited. This study recruited participants from a larger clinical trial, thus was dependent on recruitment to the larger trial. Over the course of recruitment 63 participants were recruited into the FAST INdICATE trial at the Norfolk site, 62% were eligible to participate in TMS. Of the participants that were invited to participate in the additional TMS, 68% of them agreed take part.

The amount of upper limb use prior to TMS assessment was not controlled for. Participants completed upper limb motor assessments (45-60 minutes of upper limb use) prior to session one but not session two. However, this study was designed to be pragmatic; if TMS is to be used in the clinical setting it is unlikely that the amount of upper limb use will be controlled for prior to TMS assessment.

5.5 Conclusions

In summary the test-retest reliability is variable ranging from good to poor in this sample of stroke survivors early after stroke. The reliability could have been influenced by many factors such as physiological changes within the CNS early after stroke, amount of upper limb use prior to TMS assessment, neural plasticity, task-dependent re-organization, time period between assessments, and TMS methods utilized. Further investigation in the reliability of TMS measures within this population, the methods used, and the target muscles of investigation is needed.

6 Discussion

The studies within this thesis addressed the need for a better understanding of the neuro-biomechanical correlates of reach-to-grasp. This knowledge can be used to develop more sensitive and targeted upper limb rehabilitation interventions.

6.1 Summary of results

The first research question was:

"Are the kinematic characteristics during reach-to-grasp different between stroke survivors and neurologically intact control participants and are the kinematic differences influenced by task requirements such as object placement?"

The first research question was addressed through a systematic review of the literature and meta-analysis. The results of the meta-analysis demonstrated that stroke survivors exhibit lower peak velocity; longer movement time; more segmented movement; increased reach-path curvature; increased trunk contribution and decreased elbow extension during reach-to-grasp in the anterior workspace compared to neurologically intact control participants. The studies included in the meta-analysis demonstrated unclear and high potential risk of bias, it may therefore be possible that there is bias in the results. The new knowledge derived from the meta-analysis is that the kinematic differences between stroke survivors and neurologically intact controls are consistent when reaching in the ipsilateral or central workspace. The findings suggest that object location does not alter the differences in kinematic characteristics during reach-to-grasp. This finding will allow therapists to focus on other aspects of reach-to-grasp such as movement speed to maintain complexity and challenge.

The second research question had two parts:

a) **"Is TMS measurement of corticospinal pathway excitability reliable (test-retest reliability) in neurologically intact adults of all ages (≥ 18 years of age)?"**
b) **"Is the reliability of TMS measurement influenced by age, gender, physical activity or dexterity?"**

The second question of this thesis was addressed through a prospective observational test-retest reliability study of TMS measures of corticospinal pathway excitability in neurologically intact adults of all ages. The reliability of TMS measures was variable; the lower end of the 95% CI was below the level of acceptable reliability (ICC < 0.70) for most measures. The 95% CI and 95% LOA were wide further indicating imprecision in the measurement. The Bland-Altman plots overall demonstrated random error in

measurement between tests. However, MEP amplitude demonstrated a trend towards a greater difference in amplitude between sessions the larger the amplitude. The motor threshold demonstrated the highest ICC values (ICC=0.547 (0.322, 0.714) to ICC=0.776 (0.639, 0.865), whereas the average MEP amplitude and the recruitment curve. Older adults (greater than 50 years of age) demonstrated wider confidence intervals and LOA compared to the groups as a whole indicating greater variability in response to TMS. The subgroup analysis of men and women did not demonstrate any differences in the reliability between the two groups. Both men and women demonstrated variability in reliability.

The third research question was:

"Is TMS measurement of corticospinal pathway excitability reliable (test-retest reliability) in a group of sub-acute stroke survivors?"

The third research question of this thesis was addressed through a prospective observational test-retest reliability study investigating the reliability of TMS measures of corticospinal pathway excitability in stroke survivors in the first three months after stroke. The findings demonstrate variable reliability; the lower end of the CI was below acceptable reliability (ICC < 0.70) for most measures. Similar to the study in neurologically intact adults, the 95% CI and 95% LOA were wide, further indicating imprecision in measurement. Overall, the Bland-Altman plots demonstrate random error in agreement between sessions for most measures. However, the MEP amplitude and latency demonstrated a trend for a greater difference between sessions, the larger the amplitude, and the longer latency (ECR and APB); this is similar to the findings in the neurologically intact adults. The stroke survivors' results demonstrated wide confidence intervals and LOA compared to the group of neurologically intact control participants suggesting greater variability in corticospinal pathway excitability and imprecision in measurement.

6.2 All findings in the context of the literature

6.2.1 Reach-to-Grasp

A starting place for improving upper limb rehabilitation interventions is a better understanding of the neuro-biomechanical correlates of reach-to-grasp. The systematic review identified kinematic characteristics that are consistently different between stroke survivors and neurologically intact control participants during reach-to-grasp in the central and ipsilateral workspace. The kinematic characteristics identified in the present review are in line with conclusions of previous narrative reviews; such as stroke survivors demonstrate lower peak velocities, longer movement times, and decreased smoothness of movement compared to control participants (Alt Murphy and Häger, 2015, McCrea et

al., 2002, van Vliet et al., 2013). Previous reviews have combined the kinematics of reach-to-grasp with reach-to-target when examining the differences between stroke survivors and neurologically intact adults (Alt Murphy and Häger, 2015). However, there is evidence that upper limb kinematics are different during goal oriented reaching such as reach-to-grasp (Wu et al., 2000), thus suggesting the kinematics of reach-to-grasp and reach-to-target should be synthesised separately. The meta-analyses conducted in this review extends the findings of the narrative reviews by providing novel evidence that object location in the central or ipsilateral workspace does not change the differences in kinematics of movement between stroke survivors and neurologically intact adults. Therefore therapists can focus on other aspects of the reach-to-grasp task to maintain challenge and complexity.

The reach path ratio was not significantly different between stroke survivors and neurologically intact control participants during reach-to-grasp in the central workspace. A reach in the central workspace combines shoulder flexion and adduction with elbow flexion, this combination of joint movements is part of the flexor synergy pattern, and an easier combination of joint movements for stroke survivors (Cirstea and Levin, 2000). Additionally, a reach in the central workspace requires a more curved path to reach the object compared to reach in the ipsilateral workspace in which the arm extends in a straighter path. The specific joint combinations and more curved reach path to the object during reach in the central workspace may have contributed to the non-significant findings in the meta-analysis.

Movement smoothness was not significantly different between stroke survivors and neurologically intact control participants when reaching in the ipsilateral workspace. There were two studies that assessed movement smoothness in the ipsilateral workspace, one demonstrating statistically significant findings the other demonstrating non-significant findings, both with relatively small sample sizes. It is possible that the limited number of studies (two) in the meta-analysis did not provide enough participants to examine a potential difference in kinematics.

The studies included in the review demonstrate unclear or high potential risk of bias, thus there is the potential that the findings of the meta-analyses also contain bias. There was insufficient attempt to blind assessors. The kinematic outcomes measures are less susceptible to assessor bias, however the potential for bias remains due to an interaction between the assessor and the participant. The blinding of assessors is a key component of potential risk of bias assessments and a possible confounder.

There was substantial heterogeneity between studies such as type of reach-to-grasp task, upper limb motor ability, time since stroke, movement speed, trunk restraint, and

methods of data collection and analysis. The heterogeneity may allow the results of the meta-analyses to be generalizable to the wider stroke population. However, standardisation of reach-to-grasp tasks would be advantageous in future research. The standardisation of reach-to-grasp tasks would ease direct comparisons in kinematics between studies, and may make kinematic analysis more applicable in the clinical setting.

6.2.2 **Upper limb motor function**

The stroke survivors included within the studies in the systematic review and in the TMS reliability study demonstrated a range of upper limb motor function. Many studies in the systematic review did not include subgroup distinction based on upper limb motor function.

There are findings that suggest stroke survivors with moderate motor deficits demonstrate different kinematics to those with mild motor deficits, such as longer movement time and decreased elbow extension (Alt Murphy et al., 2011, Roby-Brami et al., 2003b), lower peak velocity (Alt Murphy et al., 2011) and greater trunk displacement (Alt Murphy et al., 2011, Levin et al., 2002, Michaelsen et al., 2004, Roby-Brami et al., 2003b, Roby-Brami et al., 2003a, Roby-Brami et al., 1997). However, the findings of the present sensitivity analysis (in the systematic review) demonstrated that when participants with mild motor deficits and moderate motor deficits were removed from the meta-analysis the differences in kinematics did not change. However, the confidence intervals of the stroke survivors with mild motor deficits were narrower than those with moderate motor deficits (e.g. sensitivity analysis of peak velocity, movement time, and trunk contribution) suggesting that stroke survivors with moderate motor deficits have greater movement variability.

The increased movement variability in stroke survivors with moderate to severe motor deficits may be due to degrees of freedom available, decreased muscle strength, and utilising different joint combinations. These factors that contribute to impaired movement may be due to decreased or fluctuating corticospinal pathway input to the muscles of the paretic upper limb. The confidence intervals and limits of agreement of the reliability of TMS measures were wider for the stroke survivors compared to neurologically intact adults. For example, in the neurologically intact participants the non-dominant biceps RMT ICC=0.756 (0.599, 0.858), and the 95% LOA= -9.466 to 9.027 (% of stimulator output); compared to stroke survivors the non-paretic biceps RMT 95% ICC=0.434 (0.066, 0.698), 95% LOA= -20.053 to 20.853 and paretic biceps 95% ICC=0.665 (0.337, 0.851), 95% LOA= -26.230 to 20.659. The range of differences between sessions for stroke survivors was greater than 10% of stimulator output compared to neurologically intact adults.

The greater variability observed in stroke survivors movement and corticospinal pathway excitability may be due to the differences of upper limb motor function between participants, size and exact location of the stroke, and amount of corticospinal damage. It is known that stroke survivors with poorer motor function have greater damage to their corticospinal pathway (Feydy et al., 2002, Ward and Cohen, 2004, Talelli et al., 2006). Furthermore, stroke survivors with poorer motor function exhibit increased bilateral activation during movement, greater recruitment of ipsilateral pathways, and possibly recruitment of alternative pathways (reticulospinal pathway) (Calautti et al., 2001, Feydy et al., 2002, Turton et al., 1996, Jankowska and Edgley, 2006). This suggests that stroke survivors with poorer motor function may demonstrate inconsistent corticospinal pathway excitability contributing to variability in movement kinematics and TMS measurement. The confidence intervals related to the systematic review and TMS reliability as well as the LOA were wider for the stroke survivors compared to neurologically intact adults. The data regarding upper limb motor function of the stroke survivors in the TMS reliability study can be investigated at the conclusion of the FAST INdICATE trial when data analysis can commence.

6.2.3 **Older adults**

Differences exist in the classification of older adults between studies, as well as inconsistent age-matching of neurologically intact control participants in the studies included in the systematic review. The different classifications of older adults complicates direct comparisons between studies and to stroke survivors of whom many are older adults; the mean age of a stroke survivor is 75 years of age (Stroke Association, 2013).

Neurologically intact control participants in the primary studies included in the systematic review were not consistently age matched to the stroke survivors potentially biasing the findings of the meta-analyses. Utilizing age-matched control participants is important as upper limb biomechanics changes from around age 50 (Barnes et al., 2001, Rundquist et al., 2009). The risk of stroke increases with age from 50 years, and the mean age of a stroke survivor is 75 years (Xanthakis et al., 2014, Stroke Association, 2013); thus comparing the kinematics of stroke survivors to younger adults may have a potential impact on the kinematic differences found. For example, if neurologically intact older adults move at a reduced speed and use different joint motions (compared to younger adults) the findings of the meta-analyses could have overestimated the differences in kinematics, thus potentially inducing bias in the findings.

The ICC values of older adults in comparison to previous studies of older adults are comparable for some measures, such as the slope of the recruitment curve (Schambra et al., 2015); and lower for other measures such as the motor threshold (Schambra et al.,

2015) and MEP amplitude (Christie et al., 2007). The previous TMS test-retest reliability studies included “older” participants however the term “older” was quantified differently. The present thesis classified individuals 50 years of age and older as “older”, compared to other studies classifying individuals as older if greater than 40 years of age (Schambra et al., 2015) and if greater than 65 years of age (Christie et al., 2007). Age-related changes in the corticospinal pathway (decreased myelination) were present comparing adults 21-37 years of age (young) to adults 42-59 years of age (middle aged), and there were further decreases in myelination noted in adults 65-76 years olds (older-adults) (Salat et al., 2005). The varied age threshold used to determine “older” adults may be a contributing factor to the differences in the ICC values between studies.

The older adults in the present thesis also exhibited wider confidence intervals and limits of agreement in comparison to the group as a whole in some MEP elements. The dominant biceps AMT for the whole group was ICC=0.757 (0.612, 0.854), 95% LOA= -9.303 to 10.895 (% stimulator output), whereas older adults ICC=0.651 (0.250, 0.857), 95% LOA= -10.275 to 14.608 (% stimulator output). On the other hand, for the average MEP amplitude of the non-dominant APB assessed at 120% AMT for the whole group the ICC=0.506 (0.272, 0.685), 95% LOA -3.929 to 5.282, which exhibits wider CI and LOA than the older adults which have an ICC=0.750 (0.440, 0.899), 95% LOA=-3.645 to 4.150. The variability demonstrated may be partly due to deceased myelination of the corticospinal pathway neurons (Salat et al., 2005), resulting in differing numbers of neurons being activated by the TMS stimulus. The activation of different groups of neurons may lead to variable corticospinal response to the TMS stimulus and decreased measurement agreement between sessions. The varying reliability for the different elements in older adults compared to the whole group suggests a more specific use of TMS may be needed. Specific TMS measures may be better suited for specific age groups to examine the corticospinal pathway. Future investigations with a larger sample of middle age to older adults and further distinction between age groups is needed.

6.2.4 **Stroke survivors**

Overall, the ICC values found for the stroke survivors in this thesis demonstrated wider confidence intervals and 95% limits of agreement compared to the neurologically intact adults in this thesis. Additionally, the ICC values for the stroke survivors in this thesis were lower compared to reliability findings in chronic stroke survivors for most measures (Koski et al., 2007a, Liu and Au-Yeung, 2014, Schambra et al., 2015). The ICC values for the slope of the recruitment curve were comparable to previous research in sub-acute stroke survivors (Schambra et al., 2015). The difference in ICC values found in this thesis compared to research in chronic stroke survivors may be due to fluctuations in corticospinal pathway excitability that are a result of the physiological processes

occurring in the first few months after stroke. The physiological processes are the initial inflammatory response; immune response; spontaneous recovery; hyper-excitability within the motor areas and accelerated motor recovery (Wahl and Schwab, 2014, Que et al., 1999, Redecker et al., 2002, Marshall et al., 2000, Kwakkel and Kollen, 2013, Calautti et al., 2001, Cramer, 2008). Daily assessment of the corticospinal pathway in the first few weeks after stroke demonstrated significant differences in the active motor threshold between days, as well as substantial variability within subject and between subject variability (Swayne et al., 2008). The physiological processes and the significant differences in motor (Liepert et al., 2000b) threshold suggests that the corticospinal pathway may exhibit fluctuating excitability, neural plasticity may be reflected in TMS measurement and subsequently the ICC values as well as the 95% confidence intervals and the LOA.

The ICC values for the paretic muscles (lesioned hemisphere) were higher than the non-paretic muscles (non-lesioned hemisphere) for motor threshold, silent period and MEP max. On the other hand, the silent period demonstrated lower ICC values compared to stroke survivors greater than six months after stroke (Wheaton et al., 2009, Liu and Au-Yeung, 2014). The higher ICC values for paretic muscles are similar to the findings of Koski et al (2007), alternatively, there is evidence of lower ICC values in the lesioned hemisphere (Hoonhorst et al., 2014). The higher ICC values in the lesioned hemisphere may be related to the non-lesioned hemisphere exhibiting cortical disinhibition early (13.8±4.6 days) after stroke (Liepert et al., 2000b), shifting activation to the non-lesioned hemisphere (Marshall et al., 2000, Tombari et al., 2004). The increased activation of the non-lesioned hemisphere may contribute to variability in corticospinal pathway excitability and thus the lower ICC values in the non-paretic upper limb as well as for the silent period which is a measure of intra-cortical activity. Future research investigating cortical inhibition in conjunction with single pulse measurements could provide knowledge of the cortical processes contributing to the variability of TMS measurement.

Overall, the biceps muscle of stroke survivors tended to demonstrate lower ICC values compared to the distal muscles (ECR and APB). This is possibly due to fluctuations in corticospinal connections related to motor recovery. There is evidence that upper limb stroke recovery occurs in a proximal to distal gradient (TTl, 1951). Conversely, there is also evidence that the emergence of a biceps MEP was not different to the emergence of a FDI MEP (Schambra et al., 2014). Despite not finding a difference in emergence of the MEP; in the present study the MEP was already present. The Bland-Altman plots of the paretic biceps muscle demonstrate a greater number of differences in measurement are below the mean difference line indicating the amplitude was larger the second session, which may potentially be reflecting neural plasticity. Thus, the biceps may have

potentially been receiving greater corticospinal input, or variable corticospinal input related to motor recovery; which contributed to the lower ICC values.

In the present study the interval between assessments (one to three days) to determine the test-retest reliability of TMS measures in stroke survivors was potentially too long, contributing to neural plasticity being reflected in the measurement. The Bland-Altman plots of the paretic biceps muscle demonstrate a greater number of differences below the mean difference line suggesting larger MEP amplitudes at the second session. The ICC values of the motor threshold found in the present study were lower than previous studies of sub-acute stroke survivors (Schambra et al., 2015) in which the interval between assessments was one day. There is evidence of significant day to day changes in the active motor threshold in the first weeks after stroke (Swayne et al., 2008). Furthermore, one day of physical therapy has been associated with an increase in muscle motor map area (Liepert et al., 2000a). It may be possible that during the three days between assessments the corticospinal pathway excitability changed as a result of participation in rehab and was reflected in the reliability of TMS measurement.

6.2.5 **Women**

The present study included participants ≥ 18 years of age and both men and women. The ICC values exhibited in this thesis demonstrate that women tended to have lower ICC values for some measurements, such as motor threshold and MEP amplitude, compared to men. There is evidence that women demonstrate greater variability in response to TMS compared to men (Pitcher et al., 2003, Smith et al., 2011). It is thought that the increased variability found in women is due to female hormones during the menstrual cycle and menopause such as progesterone (Smith et al., 2002, Smith et al., 1999, Wassermann, 2002). Progesterone is associated with GABA which acts as an inhibitory neurotransmitter during the menstrual cycle phase, when progesterone is high, there is greater inhibition in response to paired-pulse TMS (Smith et al., 1999). In a group of older and younger men, there was no difference in the motor threshold, MEP amplitude or slope of the recruitment curve between the groups (Smith et al., 2011). It is possible that some of the women were in the high progesterone phase of their menstrual cycle at one of the testing sessions, potentially influencing the agreement between tests. Additionally, the menopausal women may have had low levels of progesterone influencing their response to TMS and possibly the reliability. The hormones may affect specific TMS measures such as motor threshold and MEP amplitude but have less influence on MEP latency. This would be of interest to investigate in a larger population of women.

6.2.6 **Target muscle of investigation**

The reliability of the MEP elements differed between muscles for both neurologically intact adults and stroke survivors, which is similar to findings of previous reliability studies (Malcolm et al., 2006, Kamen, 2004, Carson et al., 2013). The biceps muscle demonstrated higher estimated ICC values for the motor threshold and lower estimated ICC values for MEP amplitude for the neurologically intact individuals, whereas the distal muscles demonstrated higher ICC values for the stroke survivors across all measures. The ECR demonstrated the most consistent ICC values across all MEP elements for both neurologically intact adults and stroke survivors.

It is known that the individual muscles of the upper limb respond differently to brain stimulation (Martin et al., 2006). It may be possible that specific MEP elements are more reliable in specific muscles, warranting further research.

6.2.7 **Upper limb use**

The amount of arm use prior to TMS assessment could have contributed to the variability in TMS measurement in both stroke survivors and in the neurologically intact adults. It is known that arm use can change the excitability of the corticospinal pathway (Pascual-Leone et al., 1995); and task-dependent neural re-organisation (rehabilitation) can be reflected in TMS measurement (Koski et al., 2004, Liepert et al., 2000a, Brouwer and Schryburt-Brown, 2006). The amount of arm use prior to TMS assessment was not controlled for in this thesis.

The stroke survivors participated in clinical assessment of upper limb motor function (45-60 minutes of arm activity) prior to TMS assessment at the baseline session but not at the second session. The varying amount of activity prior to TMS could have contributed to differing levels of corticospinal pathway excitability. The Bland-Altman plots demonstrate that the MEP latency of the paretic ECR tended to be shorter at the first session. The shorter latency at the first session may be due to repetitive use during upper limb assessment.

The neurologically intact adults could have been using their upper limb for typing, writing, or their occupation at different amounts prior to each TMS session contributing to varying corticospinal pathway excitability at each TMS session.

The type and amount of arm use could also have influenced the findings of the systematic review. The sensitivity analysis found no differences in the kinematics of stroke survivors early after stroke (< three months) compared to later after stroke. However, there were a limited number of studies (three) that included stroke survivors less than three months since stroke, and they all measured different kinematic characteristics. The possibility remains, that time since stroke may influence kinematics

as a result of repetitive arm use during rehabilitation. Earlier after stroke individuals are most likely participating in rehabilitation, demonstrating greater use of their paretic arm, and the rate of change in motor function is more rapid than later after stroke (Kwakkel et al., 2003). During participation in rehabilitation, participants will be focusing on re-training of reach-to-grasp and movement control of the paretic upper limb. On the other hand, later after stroke participants are less likely to be participating in a rehabilitation program and will have developed individual techniques or compensation to accomplish reach-to-grasp out of necessity, or will use their non-paretic arm because it may be quicker. There are limited studies of the kinematics of stroke survivors early after stroke. Understanding how kinematics change with recovery may provide knowledge of which interventions provide lasting change.

The amount of arm use is difficult to control for, since we use our arm and hand throughout the day for almost all activities. The use of a diary for participants to note how they used their arm and hand in the time leading up to TMS and between assessments may be a useful way to evaluate if daily arm use influences TMS measurement.

6.2.8 **Individual variability**

There is inter-individual variability in response to TMS that can contribute to the wide 95% confidence intervals and LOA. Factors that can influence inter-individual differences are BDNF (brain derived neurotrophic factor) and handedness.

Briefly, BDNF is a gene that contributes to neural plasticity and has been found to be increased in response to motor training. Individuals with a morphism to the BDNF gene demonstrate decreased neural plasticity in response to TMS and motor training (Kleim et al., 2006). Additionally, individuals with a BDNF morphism demonstrated less brain activation in response to learning a motor task, greater number of errors in the motor task, and decreased retention compared to individuals without the morphism (McHughen et al., 2010). It may be conceivable that a BDNF morphism may also influence reliable activation of the corticospinal pathway and contribute to variability in measurement.

Handedness, or limb dominance might also be a contributing factor to variability within corticospinal pathway excitability, its measurement, and movement kinematics.

This thesis demonstrated a trend towards higher estimated ICC values for the non-dominant limb motor threshold, silent period, MEP max, and MEP amplitude (biceps). Previous research has demonstrated that the coefficient of variation differed for the motor threshold and silent period of the dominant and non-dominant limbs (Koski et al., 2005). There is evidence that the dominant motor cortex demonstrates greater intercortical connections, lower motor thresholds, and varied muscle motor map size

(Hammond, 2002). These findings suggest the corticospinal pathway projections to the dominant and non-dominant limbs differ, which may contribute to variability within and the difference in ICC values.

Hand dominance can also influence movement kinematics during reach-to-grasp, and potentially the findings of the meta-analyses. The movement of the dominant limb is directed by proximal control (shoulder) compared to movement of the non-dominant limb, which is directed by elbow torque (Sainburg and Kalakanis, 2000). The neurologically intact controls used both their dominant limb (Lang et al., 2005, Michaelsen et al., 2004), non-dominant limb (Messier et al., 2006), or a mixture of both (Alt Murphy et al., 2011, Aruin, 2005) to complete the reach-to-grasp task. Comparing stroke survivors' movement to neurologically intact controls movement of the dominant limb may result in greater differences in kinematic characteristics compared to the non-dominant limb. Therefore, utilising the dominant limb may potentially overestimate the findings of some studies, and contributing to potential bias in the findings of the meta-analyses.

6.2.9 **MEP facilitation**

TMS data collected during background contraction can influence the motor threshold; MEP amplitude; MEP latency and the silent period can influence individual muscles differently.

The reliability study of TMS measures in stroke survivors did not designate a specific percentage of muscle contraction to maintain during data collection. Participants were instructed to maintain a slight contraction which was monitored by the researcher. Despite not maintaining a specific muscle contraction, stroke survivors' estimated ICC value was comparable to neurologically intact controls for the active motor threshold, silent period, and the recruitment curve. However, the estimated ICC values were lower for other measures. It may be possible that fluctuating level of background contraction contributed to the lower ICC values as well as wider confidence interval and 95% LOA demonstrated in the stroke survivors.

The ICC values in this thesis demonstrated higher estimated ICC values of MEP amplitude measured during active contraction compared to values at rest for both stroke survivors and neurologically intact control participants. These results are comparable to previous studies of long-term reliability of MEP amplitude. However the short-term reliability demonstrated the opposite effect (higher ICC values for the resting MEP amplitude) (Ngomo et al., 2012). The Bland-Altman plots for both neurologically intact adults and stroke survivors demonstrate that with increasing average MEP amplitude there is a greater difference between measurements. This suggests there may be an

association between the agreement between sessions and the magnitude of the measurement, warranting investigation in the future.

There is evidence that maintaining background contraction during data collection decreases fluctuations in corticospinal excitability, decreases sub-threshold muscle activation, and focuses attention to the task (standardised attention across all participants) (Kiers et al., 1993, Koski et al., 2007a, Darling et al., 2006). The variability in MEP amplitude decreases with increasing muscle activation (5% to 10% MVC) and the intensity of the stimulus (Darling et al., 2006, Pitcher et al., 2003). The trend for decreased variability at higher stimulus intensity was only weakly demonstrated by the dominant ECR, non-dominant APB and paretic APB in this thesis. With increasing stimulus intensity, neurons that are farther from the stimulus will be activated (Chen, 2000). It may be that the distant neurons are not reliably activated contributing to the variability demonstrated at higher stimulus intensities for some muscles in this thesis.

The motor threshold may also be a possible contributing factor to variability of MEP amplitude. Previous research has demonstrated that individuals with lower resting motor thresholds demonstrated greater MEP coefficient of variation within the recruitment curve (Smith et al., 2011). The motor threshold in association with MEP variability was not explored in the present study. However, it may be possible that individuals with lower motor thresholds exhibited greater MEP amplitude contributing to low ICC values and wide 95% CI as well as 95% LOA.

The relationship between motor threshold; strength of background contraction; strength of stimulus intensity and variability of MEP amplitude should be explored in future research to better understand corticospinal pathway excitability and factors that may influence the reliability of MEP amplitude.

6.2.10 **TMS**

The reliability of MEP amplitude in the present study was below acceptable reliability for most muscles. The MEP amplitude is used to determine the motor threshold and also in plotting of the recruitment curve. Therefore if the amplitude is variable then subsequently the motor threshold and recruitment curve may also be variable. The variability of the MEP amplitude could have contributed to the variability found in the other TMS measures in this thesis.

The type of coil, neuro-navigated TMS, coil position, and current direction into the motor cortex can all influence TMS measurement and possible agreement between tests.

6.2.10.1 **TMS coil**

The MEP amplitude, latency, and silent period are susceptible to differences in measurement based on a stimulus delivered by a circular coil or a figure of eight coil, as well as current direction. Small movements of the coil and changes in current flow could have contributed to variability of TMS measures in the present study.

Previous studies used a mixture of circular coils and figure-of-eight coils. A circular coil delivers a more diffuse magnetic impulse such that small movements of the coil on the scalp will not influence the MEP size. Alternatively, a figure-of-8 coil (utilized in this thesis) delivers more focal stimulation to an area about 35 cm^2 (Wassermann, 2002, Rivadulla et al., 2014). The figure-of-eight coil is susceptible to small changes in coil position or angle during data collection which can alter the direction of current through the motor cortex activating different clusters of neurons (Conforto et al., 2004).

The circular coil more easily activates d-waves (which contribute to the MEP amplitude) compared to a figure-of-eight coil (Di Lazzaro et al., 2004). Therefore, if d-waves are more consistently activated when using a round coil the MEP amplitude may be less variable than when using a figure-of-8 coil. A figure-of-eight coil may activate d-waves when tilted (medial-lateral), but not when positioned posterior-anteriorly. Change in current direction due to coil tilt can also influence the MEP latency and the silent period. For example, current in a lateral-medial orientation decreases the latency by 1-2 ms because of easier recruitment of d-waves compared to current flow in the posterior-anterior direction (Di Lazzaro et al., 2004). The silent period is shortest when the current flows in a posterior-anterior direction (mean and SD: 108.0±38.1 ms), and longest when the current flows in the anterior-posterior direction (139.2±.30.8 ms); additionally the coefficient of variation was larger for current flow in the posterior-anterior direction CV=35.3 (versus CV=22.1 for anterior-posterior) (Orth and Rothwell, 2004). A figure-of-eight coil was used in this thesis because it delivers more focal stimulation to activate the upper limb area of the motor cortex.

The researcher held the coil in place during data collection; small movements or tilts of the coil on the head, or if the participants move their head on the coil this could have activated different clusters of neurons or d-waves. The activation of different clusters of neurons may have altered the amplitude, latency, and silent period contributing to variability in measurement within and between sessions. The accuracy of maintaining the optimal coil position may have been enhanced through the use of a coil holder.

To improve coil placement and maintain optimal coil position, neuro-navigated TMS has been used.

6.2.10.2 **Neuro-navigated TMS**

Neuro-navigated TMS combines TMS with MRI. The MRI is used to determine the "hand knob" area of the motor cortex, and once determined the researcher then uses the MRI image to guide TMS coil placement. Neuro-navigated TMS allows the individual administering the TMS to identify when the coil angle has changed so it can be repositioned to avoid changes in current flow and neuronal activation (Cincotta et al., 2010). Three studies utilized neuro-navigated TMS (Ngomo et al., 2012, Sollmann et al., 2013) and a phantom MRI image (Schambra et al., 2015).

There is evidence that using neuro-navigated TMS improves the spatial accuracy of TMS coil placement on the hotspot compared to "blind" trials in which standard methods of hot spot determination are used (Cincotta et al., 2010, Sollmann et al., 2013, Gugino et al., 2001). Similarly, MEP amplitude demonstrated a lower coefficient of variation during neuro-navigated TMS 71±14%, compared to non-navigated 91±15% (Julkunen et al., 2009). By not using neuro-navigated TMS the individual administering the TMS may not be aware of small changes or tilts of the coil that could alter current direction and activate different neurons resulting in measurement variability.

The present findings (ICC values) of the motor threshold and slope of the recruitment curve were similar to two of the studies that utilised neuro-navigated TMS (Ngomo et al., 2012, Schambra et al., 2015), whereas, the ICC values of the present study were lower than others (Sollmann et al., 2013, Schambra et al., 2015). The impact of neuro-navigated TMS on the reliability of TMS measurement warrants future research to determine its benefit; as some ICC values are comparable to studies without neuro-navigated TMS.

6.2.11 **Hot spot and motor threshold determination**

The hot spot can be determined utilizing visual assessment of the MEP on the EMG or using a standard position five cm lateral to the vertex; the first method has demonstrated lower motor thresholds (Conforto et al., 2004). The benefits of using a standard coil position are that the same group of neurons will be activated every time, however a limitation is that the standard position may not be the optimal position to collect data for a specific muscle, as each muscle representation is a specific location in the motor cortex. Previous studies have used the same hot spot for all sessions (Cacchio et al., 2011), whereas others determined the hot spot each session (based on MEP on EMG) (Koski et al., 2007a, Liu and Au-Yeung, 2014). Arm use can influence corticospinal pathway excitability, thus determining the hot spot at each session may be more representative of the optimal location to collect data which may fluctuate over the course of the day. However, determining a new hot spot each session will result in different groups of neurons being activated which may have contributed to variability in MEP amplitude and

motor threshold in the present study. The differing methodologies complicates comparison between studies because different groups of neurons will be activated.

The processes used to determine the motor threshold in the present study could have contributed to the variability, and measurement agreement between sessions. The processes implemented to determine a motor threshold were in line with previous research using the presence of an MEP in half of successive trials > 50mV resting threshold, and > 200 mV for active threshold (Rossini and Rossi, 2007, Koski et al., 2007a). However, the program used to collect MEPs did not provide an exact value of milliamps of the MEP. Hence, it is possible that a true motor threshold was not found, thus contributing to the variability between sessions.

6.2.12 **Methods of data processing and analysis**

6.2.12.1 **Intraclass correlation coefficient**

The ICC is a useful measurement of reliability, however there are also limitations. The ICC can be influenced by interpretation, model used, population being studied, variance within the population, and the range of the scale of measurement (de Vet et al., 2006, Portney and Watkins, 2009, Müller and Büttner, 1994).

Firstly, assigning a value of acceptable reliability (ICC>0.70) was arbitrarily selected and has no absolute meaning in terms of the measurement used (de Vet et al., 2006, Portney and Watkins, 2009, Müller and Büttner, 1994). There are different values that can be used to determine acceptable reliability; assigning a different value would change the interpretation of the reliability and the results. For example, Eliasziw and colleagues (1994) suggested interpretation of the ICC as follows: 0.0-0.2=slight, 0.21-0.40=fair, 0.41-0.60=moderate, 0.61-0.80=substantial, 0.81-1.00=almost perfect reliability (Eliasziw et al., 1994). Had the ICC values been interpreted in this way in the present study the interpretation of the reliability would have been different. An ICC > 0.70 was selected as acceptable reliability because it has been commonly used in previous TMS reliability research (Schambra et al., 2015, Malcolm et al., 2006). However, if previous research utilised a different interpretation the findings of the reliability of this thesis may be comparable.

Secondly, the ICC is sensitive to “unreliable” measurements, which can lower reliability by lowering the ICC value (closer to 0) (de Vet et al., 2006, Müller and Büttner, 1994, Portney and Watkins, 2009). The Bland-Altman plots demonstrated some differences in agreement between sessions were very far from the mean difference, potentially greater than three standard deviations from the mean. It may be possible that the differences far from the mean difference contributed to lower ICC values in this thesis.

Thirdly, the ICC is sensitive to the measurement scale of the tool being investigated; the wider the range of measurement the higher the ICC values (Müller and Büttner, 1994). Muller and Buttner (1994) use the example of measuring blood pressure. Systolic blood pressure has a wider measurement range compared to diastolic blood pressure. The ICC values for measuring systolic blood pressure are therefore higher giving the impression that diastolic blood pressure is more difficult to assess, which is not the case (Müller and Büttner, 1994). The narrow measurement range of the MEP elements could have contributed to the lower ICC values. For example the MEP latency and silent period are measured in milliseconds, a change of a few milliseconds may influence the agreement between sessions. However, it is likely the measurement range may have also influenced the reliability of earlier studies, and thus may not be a contributing factor to the ICC values found in this thesis.

Finally, the ICC model used can influence reliability and the ICC values. The ICC model [2,k] is the reliability of the mean of observations; whereas ICC model [2,1] is the reliability of individual observations (Portney and Watkins, 2009). Model ICC [2,1] can be influenced by systematic differences inherent in measurement error; whereas model ICC [2,k] does not account for systematic differences (de Vet et al., 2006). Therefore the ICC values resulting from model ICC [2,1] will be lower than those of ICC [2,k] (de Vet et al., 2006, Portney and Watkins, 2009). This is important to note when interpreting ICC values as well as comparing the ICC values between studies. The ICC model used in the present study was ICC [2,1] which demonstrated lower ICC values than research that utilised model ICC [2,k] (Schambra et al., 2015, Malcolm et al., 2006). It may be the ICC model used is contributing to the difference in ICC values between studies, not the agreement between tests. Furthermore previous studies did not consistently report the ICC model used (Ngomo et al., 2012, Christie et al., 2007) or the associated 95% confidence intervals (Carroll et al., 2001, Ngomo et al., 2012).

The confidence interval is a measure of the variance in measurement (de Vet et al., 2006), thus it should be provided to fully interpret the reliability. To have confidence in a measure there should be agreement between measurements and the variance of the agreement should be within specific limits. The lower end of the confidence interval should be within the range of acceptable reliability to have confidence in the result (Portney and Watkins, 2009). This can impact health research and the use of specific measures to assist in clinical decision making. For example the presence of an MEP in conjunction with active movement is used to predict upper limb functional outcomes after stroke and possibly to determine level of care such as rehabilitation (Stinear et al., 2012, Hendricks et al., 2002). However, if single measurements of the MEP are variable early after stroke as the present results suggest, and significant differences in motor threshold

have been identified in daily assessment early after stroke (Swayne et al., 2008) possibly more than one TMS assessment is needed to predict motor function. The lack of reporting of confidence intervals may potentially lead to overestimating the reliability of a measure or measurement tool, its usefulness in the clinical setting, and comparisons between studies variance is not possible.

6.2.12.2 **Electrode placement**

The placement of the surface electrodes in the optimal position to monitor muscle activity is essential to data collection (Wassermann, 2002), thus if electrode placement differs between sessions, then the muscle activity recorded will be different and may contribute to variability in measurement. For example, the EMG activity of the biceps was recorded using surface electrodes placed in the middle, upper, and lower sections of the muscle belly. The lower section of the muscle was found to demonstrate the greatest muscle activity; and muscle activity decreased as electrode placement became more proximal (Ahamed et al., 2012). Exact electrode placement was attempted at both sessions. However if the electrodes were placed slightly proximal, the muscle activity recorded may have been different, possibly contributing to variability in the measurement. Electrode placement can also influence data collection in the hand muscles.

The hand muscles are small, the muscles and motor units are densely packed (Malcolm et al., 2006). The electrodes over the APB had a small inter-electrode distance, thus the possibility of cross-talk arises (Konrad, 2005). Cross talk can result in the surface electrode reading if the muscle activity of an adjacent muscle is measured (Farina et al., 2004). Cross talk can contribute to varying muscle data and possibly varying amplitude between TMS stimuli if different muscles are being recorded, since different muscles respond differently to TMS (Martin et al., 2006). The surface electrodes on the APB and ECR demonstrate greater likelihood of cross talk due to close proximity of adjacent muscles, which may have contributed to the variability in MEP amplitude and TMS measurement of the APB and ECR.

6.2.12.3 **Silent Period**

The reliability of the silent period in the present study was poor to moderate for both stroke survivors and neurologically intact adults. The ICC values of the biceps muscle was comparable to previous studies of the biceps (Harris-Love et al., 2013); the reliability of the ECR and APB were lower than previous studies (Koski et al., 2005, Cacchio et al., 2009, Liu and Au-Yeung, 2014). The differences in ICC values may be due to the methods used to determine the duration of the silent period.

The start of the silent period can be defined as the start of the MEP (e.g. Koski et al., 2005, Damron et al., 2008) or from TMS stimulus (e.g. Koski et al., 2007, Cacchio et al., 2009,). The start of the TMS stimulus is constant (0.00 milliseconds) whereas the start of the MEP varies. The silent period can be determined visually or mathematically. Damron (2008) demonstrated that visual analysis of the silent period was as reliable as mathematical analysis (running a script) $r > 0.96$; the coefficient of variation was similar CV=16.0% (visual assessment) and CV=16.5% (mathematical assessment) (Damron et al., 2008). Despite the CV being similar for visual and mathematical assessment there is the potential for assessor error during visual assessment.

In the present study the MEP latency and the silent period were assessed visually. To determine the MEP latency a cursor was placed at the onset of the MEP. The time from TMS stimulus (0.00 seconds) to onset of MEP was the MEP latency in ms. The duration of the silent period was determined as MEP onset to the return of EMG.

To account for potential human error, a second researcher with TMS experience independently assessed the MEP latency and silent period of 10% of trials. The researchers were in agreement within two milliseconds 84% of the time. It is likely there was an element of human error in visual assessment contributing to the wide 95% CI and 95% LOA as well as the reliability of the measurement. Likewise, the test-retest reliability of MEP latency was below acceptable reliability for most muscles; therefore if the starting point of silent period measurement was not reliable this could have influenced the reliability of silent period. Further research in the reliability of visual assessment of MEP latency and the silent period would be beneficial in determining optimal methods of data analysis.

6.2.12.4 **Recruitment Curve**

The ICC values of the slope of the recruitment curve in the present thesis were below acceptable limits (ICC < 0.70) for all muscles in both neurologically intact individuals and stroke survivors. The slope of the recruitment curve was comparable to a previous investigation in older adults (Schambra et al., 2015), however the present finding were lower than previous studies (Malcolm et al., 2006, Liu and Au-Yeung, 2014, Koski et al., 2007a, Carroll et al., 2001). The low ICC values for the slope of the recruitment curve could be due to the variability in MEP amplitude found within the present sample (Malcolm et al., 2006). The reliability of MEP amplitude was below acceptable levels for most intervals of the recruitment curve. The MEP amplitude is the basis for plotting the recruitment curve, if the amplitude is variable than the relationship between the amplitude and stimulator output may also be variable.

The recruitment curve is traditionally fitted with a sigmoidal function (Carroll et al., 2001, Carson et al., 2013, Malcolm et al., 2006) which is based on the concept of least squares taking the shape of an "s" curve (Massie and Malcolm, 2013). In this thesis not all of the participants' recruitment curve data were able to be fitted with a sigmoidal function. The sigmoidal function was able to be fitted for neurologically intact individuals resting biceps in 10% of participants, active biceps=60%, resting ECR=29%, active ECR=45%, resting APB=31%, active APB=57% of participants; and for stroke survivors non-paretic biceps=35%, paretic biceps=4%, non-paretic ECR=8%, paretic ECR=18%, non-paretic APB=32%, and the paretic APB=30%. The percentage of participants that could not be fitted with a sigmoidal function was higher in the present study than earlier studies in which 5.9% of neurologically intact participants, 9.4% of subacute, and 12.7 % of chronic participants demonstrated inappropriate recruitment curve model fits (Schambra et al., 2015).

A possible reason for inappropriate fits could have been enough data points due to some stimulation intensities were above 100% of the stimulator output or high stimulation intensities were uncomfortable. Furthermore, not all individuals demonstrated an increase in MEP amplitude with increasing intensity (neurologically intact participants: biceps rest n=7, active n=11, ECR rest n=7, active n=15, APB rest n=2, active n=19: stroke survivors non-paretic biceps 7/26, non-paretic ECR n=5/26, non-paretic APB 4/25, paretic biceps n=8/25, paretic ECR n=6/22, and paretic APB n=3/20). The recruitment curve obtained in the stroke survivors and in the active conditions of the neurologically intact participants included 100%, 110%, 120%, 130% of AMT. It may be possible that there were not enough intervals in the recruitment curve to collect sufficient data. Potentially including 90% in the active conditions as was done during the resting conditions, or increasing in 5% increments, might have improved the plotting of the recruitment curve. The lack of increasing amplitude could be due to small movements of the coil or participant head movement changing the direction of current and activating different clusters of neurons varying the MEP amplitude. The stroke survivors may have been experiencing fatigue from generating a muscle contraction thus their contraction could have become weaker towards the end of the recruitment curve. If there was less corticospinal pathway excitability (decreasing strength of muscle contraction) the MEP would not have increased.

Previous studies also reported inappropriate model fits using the sigmoidal function (Schambra et al., 2015, Massie and Malcolm, 2013, Ray et al., 2002). An alternative to the sigmoidal curve is to fit the data with a linear regression using the line of best fit (Koski et al., 2007a, Massie and Malcolm, 2013, Ward et al., 2007). There is evidence that a linear function was the most valid and accurate fitting of the recruitment curve for

the biceps and the APB (Ray et al., 2002). In contrast, there is evidence that sigmoidal curves best fit the recruitment curve of hand muscles, and linear functions are a better fit for other muscles (Siebner and Rothwell, 2003). The peak slope of the sigmoidal function has been found to be correlated (r=0.9) with the linear slope of the linear function (Massie and Malcolm, 2013).

The benefits to using a linear regression are that it requires less data points which may be of use in stroke survivors with decreased corticospinal pathway excitability when the upper end of the recruitment curve may be above the stimulator output (Massie and Malcolm, 2013, Ray et al., 2002). In the present study data up to 130% of AMT was unable to be collected for all stroke survivors. Data up to 130% of AMT was not collected for the paretic biceps in 8/28 participants, 3/28 for the paretic ECR and 8/27 for the paretic APB because the percentage of AMT increased above the stimulator output. Some of the neurologically intact adults found the stimulus at higher intensities uncomfortable; the researcher was unable to collect data up to 130% of MT in 23/51 participants for the biceps muscle at rest, and 10/51 for the APB at rest. Therefore, incomplete data was collected in some participants. Incomplete data could have contributed to the difficulties fitting the recruitment curve with a sigmodal function.

The reliability of the recruitment curve could have been influenced by the method of curve fitting (sigmoidal versus linear), number of data points collected, the reliability of the MEP amplitude, and the associated factors that can influence MEP amplitude. The different muscles of the upper limb have different corticospinal projections, methods of data collection or curve fitting may be better if individualized to specific muscles, warranting further investigation.

6.2.13 **Reliability of physiotherapy measurement tools**

The test-retest reliability of TMS measures demonstrated in the studies in this thesis are variable, with the lower end of the confidence interval falling within the range of poor reliability. The ICC point estimates demonstrate poor to good reliability. The reliability of TMS is similar to the reliability of other measurement tools and outcome measures used in physiotherapy practice. For example the reliability of individual items on the WMFT range from an ICC of 0.50 to 0.93 (Morris et al., 2001), the reliability of manual muscle testing ICC's range from 0.69 to 1.00 (Fan et al., 2010), assessment of grip strength ICC's range from 0.68 to 0.90 (Heller et al., 1987), and the functional independence measure reliability ranges from an ICC of 0.124 to 0.661 (Kohler et al., 2009). Many studies did not report confidence intervals therefore the variability of the measurement is not known. In the context of the reliability of measurement tool available and widely used in clinical practice the reliability of TMS measurement falls within the range of reliability for measures such as the motor threshold. It may be that TMS is better suited to assess

a group as a whole versus individual change in corticospinal pathway excitability as the mean difference between tests identified by the limits of agreement was close to zero.

6.2.14 **Summary**

In summary, there are many factors that can influence measurement. The stroke location, size, and upper limb motor function may contribute to variability of movement kinematics, differences in excitability of the corticospinal pathway and subsequently in TMS measurement. The physiological processes occurring in the CNS early after stroke and in older adults, as well as gender differences due to hormones may also contribute to variability in TMS measurement as demonstrated by the wide confidence intervals and 95% limits of agreement. Furthermore, the measurement tools such as type of coil or stimulator may also influence which groups of neurons are activated by the TMS stimulus, leading to fluctuation in measurement and variable reliability.

6.3 Limitations of this thesis

The systematic review was limited to studies published in the English Language which could potentially induce reporting bias in the results. The search included multiple databases and the reference lists of relevant papers were hand searched for relevant titles; however, it is still possible that relevant studies were missed. There were challenges to the systematic review. There was unclear and high potential risk of bias in included studies which may induce bias into the results of the meta-analysis. The reach-to-grasp studies were heterogeneous utilising different tasks, objects, movement speeds, and grasps, complicating the synthesis of the findings.

A limitation of the TMS studies is the amount of upper limb use may have been different prior to the two sessions. The stroke survivors participated in upper limb motor assessments prior to TMS assessment at the first session but not the second, thus the excitability of the corticospinal pathway could have been different at the two sessions. The neurologically intact adults could have had varied upper limb use prior to the TMS sessions.

The time interval between TMS assessments for the stroke survivors could have been too long a period of time. There is evidence that one day of rehabilitation can lead to change in muscle motor map representation (Liepert et al., 2000a), and there are significant changes in motor threshold when assessed daily early after stroke (Swayne et al., 2008). A shorter time interval between assessments may have decreased the likelihood of neural-plasticity being reflected in the TMS measurement.

The stroke survivors did not use a specific percentage of muscle contraction during data collection, thus muscle activity was not standardised across all participants. There is the possibility that participants demonstrated fluctuating muscle contractions and subsequently fluctuating corticospinal pathway excitability contributing to the lower ICC values.

The test-retest reliability investigation early after stroke was underpowered; there were not enough participants included in the analysis to have statistical power. Furthermore, in the investigation of test-retest reliability in neurologically intact adults the sub-group analyses were underpowered; there may not have been enough participants to have statistical power.

The limitations of the test-retest reliability investigations of TMS are that the methods used may not be comparable with previous research and the methods may have induced

variability in the measurement influencing the reliability. Resting TMS data was only completed on the dominant limb of the neurologically intact participants.

The recruitment curve was not able to be fitted for all participants with a sigmoidal function. Data collection of additional intervals within the recruitment curve, or plotting the curve using a linear function may have improved curve fitting.

6.4 Strengths of this Thesis

The systematic review provided novel findings that object placement in the central or ipsilateral workspace does not alter kinematics of movement. This finding will allow therapists to focus on other aspects of the reach-to-grasp task to maintain complexity and challenge.

The test-retest reliability studies investigated a range of MEP elements such as the active motor threshold; resting motor threshold; MEP amplitude; MEP max amplitude; MEP latency; silent period and the recruitment curve of bilateral biceps, ECR, and APB. This was the first study to investigate the reliability of TMS measures in these muscles in a group of sub-acute stroke survivors, and one of a few studies in neurologically intact adults. This work has expanded the current reliability research which has focused solely on distal upper limb muscles. All muscles of the upper limb are essential to reach-to-grasp and functional use of upper limb, therefore understanding the corticospinal projections to these muscles is essential.

The TMS measures in the neurologically intact adults were assessed at rest (dominant limb) and during background contraction (dominant and non-dominant). The TMS data during active conditions will provide age-matched comparisons for stroke survivors in which TMS measures are often taken during background contraction to facilitate a MEP.

The reliability findings have highlighted areas in which variability may exist in TMS measurement or within the methods of data collection and analysis leading to future research questions.

6.5 Reflections on study design

Upon completion of the TMS studies, reflection of the study design and methods, and what I have learned there are aspects that could have been done differently which may improve TMS study design and implementation in the future.

Study design in the future could include investigating the test-retest reliability over three sessions in stroke survivors. The first two sessions being two consecutive days, the third session occurring a week after the first. This design would limit neural plasticity between the first and second session but allow for exploration of change in corticospinal pathway

excitability and reliability at the third sessions. The three sessions would allow for short term and longer term reliability.

The recruitment curve in the studies in this thesis did not successfully fit all participants with a sigmoidal function. Future research investigating different methods of plotting the recruitment curve (sigmoidal versus linear) and investigating the area under the curve for the different muscles of the upper limb would provide knowledge of if specific methods are better suited for specific muscles. Collecting additional data points such as increasing in 5% increments versus 10% increments (as done in the present study) or stimulating up to 150% of motor threshold if tolerated may improve curve fitting with a sigmoidal function.

It is known that strength of background muscle contraction can influence many MEP elements such as shorten the latency, decrease motor threshold, and increase amplitude (Wassermann et al., 2008, Di Lazzaro et al., 2004, Kiers et al., 1993). Furthermore, the strength of muscle contraction can influence proximal and distal muscles differently (Rösler et al., 2002, Turton et al., 1996). Utilizing different strengths of background contraction for different muscles may strengthen the study design and contribute to less variability in TMS measurement.

Assessment of background muscle contraction of the stroke survivors was completed using visual assessment, palpation, and assessment of 100 ms of EMG prior to TMS stimulus. Assessment of the maximal voluntary contraction and use of a specific percentage of muscle contraction may have decreased fluctuation of the muscle contraction and standardized corticospinal pathway excitability. A challenge of this method is that the some of the stroke survivors may have difficulty generating a maximal contraction, as well as maintaining a specific percentage of contraction due to stroke related changes in motor control and neural input (via the corticospinal pathway).

Utilizing a coil holder would improve stability of the TMS coil during data collection. This would decrease any potential movements of the coil by the researcher and may improve localization of the TMS pulse and decrease variability in measurement. Beyond a coil holder utilizing neuro-navigated TMS would provide visual confirmation of stimulation of the appropriate location which may also contribute to decreased variability in TMS measurement.

In future research applying these changes to study design may strength TMS methods and contribute to more reliable TMS measurement.

6.6 Future directions

The studies within this thesis addressed the need for a better understanding of the neuro-biomechanical correlates of reach-to-grasp, the results of which have generated directions for future research.

The systematic review highlighted the heterogeneity of reach-to-grasp tasks and literature. Progressing forward, a standardised reach-to-grasp task would be advantageous. Firstly, it would allow more direct comparisons between studies. Secondly, using a standardised task to measure change following an upper limb intervention would permit more direct comparisons between different interventions by comparing the underlying movement patterns. Future investigations utilising the kinematic differences identified in the systematic review as targets for upper limb interventions needs to be evaluated. Upper limb interventions targeted at specific movement deficits may improve the specificity of upper limb rehabilitation and decrease disability after stroke.

The reliability of the TMS measures investigated in the present thesis have expanded on previous reliability studies which focused on distal muscles, through investigating the reliability of more proximal arm muscles. This thesis found the test-retest reliability of TMS measures was variable in neurologically intact adults and in stroke survivors. The different muscles of the upper limb demonstrated varied reliability within and among MEP elements, muscles, and limbs (dominant, non-dominant, paretic, non-paretic). Future investigations examining the potential sources of variability such as target muscle, strength of background contraction, coil placement, as well as methods of data collection and analysis are needed.

Investigating the reliability of MEP elements during a range of background contractions may provide evidence of which elements are most reliable during specific muscle activation, and in a variety of muscles. Future research investigating the specificity of background contraction to individual muscles and MEP elements is needed.

One of the aims of this thesis was to investigate the reliability of TMS measures in older adults. The estimated ICC values of older adults were similar to the values for the whole group, however older adults demonstrated wider confidence intervals than the neurologically intact group as a whole for some measures. The wider confidence intervals could have been due to the smaller number of participants included in the analysis, or greater fluctuation within the corticospinal pathway with aging. Future investigations specifically in middle age and older adults and distinction between age groups would provide knowledge of how the nervous system changes over time.

Research combining the use of single pulse TMS with measures of intercortical facilitation and inhibition may provide insights into cortical processes that may influence the ICC values and variability of TMS measurement.

If TMS is to be used to assess neural plasticity within rehabilitation studies, researchers and clinicians need to know that the observed change is greater than day-today variability. Future research to determine the minimal clinically important difference of TMS measures, as well as determine if change in TMS measures is associated with change in upper limb motor function is needed.

A direction forward is a more specific use of TMS targeting specific MEP elements to measure specific muscles under specific conditions, which may be a more precise use of TMS measurement.

6.7 Concluding remarks

This thesis explored neuro-biomechanical assessment of the upper limb. The results of this thesis demonstrated that object placement in the central or ipsilateral workspace does not alter differences in kinematics between stroke survivors and neurologically intact controls. Future reach-to-grasp research would benefit from standardisation of tasks to ease direct comparisons between studies. Secondly, this thesis demonstrated that the test-retest reliability of TMS measures in neurologically intact adults and stroke survivors early after stroke is variable. There may be an association between MEP amplitude and agreement in measurement in both neurologically intact adults and in stroke survivors. The test-retest reliability findings suggest that TMS may not be suitable to detect change in corticospinal pathway excitability in individual participants. Future investigations to determine the source of variability in TMS measurement are warranted as the knowledge provided by TMS measurement is valuable in understanding motor recovery after stroke.

Appendix 1: Downs and Black Tool

Question	Rationale for Amendment
Reporting	
1) Is the hypothesis/aim/objective of the study clearly described?	
2) Are the main outcomes to be measured clearly described in the Introduction or Methods section?	
3) Are the characteristics of the patients included in the study clearly described?	
4) ~~Are the interventions of interest clearly described~~? Is the reaching task clearly defined and reproducible?	Observational studies of reaching will not include an intervention thus it is the reaching task that is most relevant for assessment.
~~5) Are the distributions of principal confounders in each group of subjects to be compared clearly described?~~ Remove	Stroke vs Healthy control
6) Are the main findings of the study clearly described?	
7) Does the study provide estimates of the random variability in the data for the main outcomes?	
8) Have ~~all important~~ adverse events/reactions that may be a consequence of the intervention been reported?	Any adverse event or reaction is important
9) ~~Have the characteristics of patients lost to follow-up been described?~~ Has loss to follow up, attrition been described?	Has attrition been described and accounted for
~~10) Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?~~ Remove	N/A as observational studies of reaching will not include risk ratios or odds ratios.
External validity	

~~11) Were the subjects asked to participate in the study representative of the entire population from which they were recruited?~~ Remove	Very similar to the next question, will only keep # 12 as it refers to the participants in the study
12) Were those subjects who were ~~prepared to participate~~ included representative of the entire population from which they were recruited? For example are participants of varying degrees of function and of varied stroke location included?	To be representative of the population of stroke survivors the sample must include those with mild to severe impairment and of varied stroke location. This will improve the generalizability of the findings of the systematic review. The control group should be made up of age matched controls to those stroke survivors as there are neuromuscular changes with age.
~~13) Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive~~ Remove	This is not relevant to a one-time assessment in a laboratory setting.
Internal validity - bias	
14) If appropriate was an attempt made to blind study subjects to the intervention they have received?	Will only be relevant to studies that are investigating a change in reaching due to an intervention, not relevant to one session observational study.
15) If appropriate was an attempt made to blind those measuring the main outcomes of the intervention?	Not applicable to instrumented measurement as it is objective and not biased such as: movement speed recorded via a motion capture system, or muscle activity recorded via EMG, or MEP recorded via TMS. In addition a researchers approach can affect behavioral outcomes, but if the same researcher completes all assessments for all participants than it would not be a confounding factor.
~~16) If any of the results of the study were based on "data dredging", was this made clear?~~ Remove	The studies included in the systematic review are experimental studies, not hypothesis testing or hypothesis driven questions such as clinical trials.
~~17) In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies,~~ Is the time period between the intervention and outcome the same for cases and controls?	Was the same protocol implemented with both the stroke participants as with the healthy controls?
18) Were the statistical tests used to assess the main outcomes appropriate?	

19) ~~Was compliance with the intervention/s reliable?~~ Was the experimental task the same for all participants?	The same reaching task and protocol implemented with both the stroke participants and healthy participants to allow comparison of reaching characteristics.
20) Were the main outcome measures used ~~accurate~~ (valid and reliable)? Were all outcome measures reported on, and no new outcome measures added in with limits, for example do the methods and results match?	Was there bias in selective reporting of results?
Internal validity – confounding (selection bias)	
~~21) Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?~~ Remove	N/A for observational studies both groups would have completed the same reaching task.
~~22) Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?~~ Remove	N/A for observational studies one-time assessment.
~~23) Were study subjects randomised to intervention groups?~~ Remove	N/A for one-time lab assessment, and both groups would be completing the same reaching task.
~~24) Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?~~ Remove	N/A participants wouldn't have been randomized for a one time observational assessment, completing the same reaching task.
~~25) Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?~~ Remove	N/A for observational studies one time instrumentation assessment.
~~26) Were losses of patients to follow-up taken into account?~~ Remove	N/A for one-time lab assessment.
~~27) Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?~~ Remove	N/A for observational studies.

Amendments to the Down's and Black tool were based on the following references: Brouwers et al 2005, Gorber et al 2007, Higgins et al 2008, Mallen et al 2006, and Monterio and Victora 2005.

Appendix 2: Modified Downs and Black Tool - for Assessment of Potential Risk of Bias

Question	YES / NO / UNCLEAR
Reporting	
1) Is the hypothesis/aim/objective of the study clearly described?	
2) Are the main outcomes to be measured clearly described in the Introduction or Methods section? • *If the main outcomes are first mentioned in the results section, the question should be answered 'no'.*	
3) Are the characteristics of the patients included in the study clearly described? • *For example: type of stroke, stroke location, time since stroke, level of current function/disability.* • *In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.*	
4) Is the reaching task clearly defined and reproducible?	
5) Are the main findings of the study clearly described? • *Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.* • *This question does not cover statistical tests which are considered below.*	
6) Does the study provide estimates of the random variability in the data for the main outcomes? *In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered 'yes'.*	
7) Have adverse events or adverse reactions that may be a consequence of the intervention been reported? Such as pain during reaching activity. • *This should be answered 'yes' if the study demonstrates that there was a comprehensive attempt to measure adverse events (a list of possible adverse events is provided).*	

Question	YES / NO / UNCLEAR
8) Has loss to follow up been described, attrition? • '*No', if attrition is not explained. 'No' if number of participants does not match the number analysed in the results. 'Yes' if mention, or not mentioned and all participants are analysed.* • *This should be answered 'yes' where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion.* • *This should be answered 'no' where a study does not report the number of patients lost to follow up.* ***External validity*** 9) Were those subjects who were included representative of the entire population from which they were recruited? • *Is the sample representative of the target population stated in the background? For example are participants of varying degrees of function and of varied stroke location included as well as age matched controls?* • *The study must identify the source population for patients and describe how the patients were selected.* • *Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists.* • *Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as 'unclear'.* • *The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.* ***Internal validity - bias*** 10) If appropriate, was an attempt made to blind study subjects to the intervention they have received? • *For studies where the patients would have no way of knowing which intervention they received, this should be answered 'yes'.* 11) If appropriate, was an attempt made to blind those measuring the main outcomes of the intervention?	

Question	YES / NO / UNCLEAR
12) Is the time period between the intervention and outcome the same for cases and controls? • *For example, was the same protocol implemented with both the stroke participants as with the healthy controls?* • *Where follow-up was the same for all study patients the answer should be 'yes'.* • *If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be 'yes'.* • *Studies where difference in follow-up are ignored should be answered 'no'.*	
13) Was the experimental task the same for all participants?	
14) Were all outcome measures valid and reliable, reported on, and no new outcome measures added in with limits? • *For example, do the methods and results match and are the conclusions supported by the findings?*	
15) Were the statistical tests used to assess the main outcomes appropriate? • *The statistical techniques used must be appropriate to the data. For example, non-parametric methods should be used for small sample sizes.* • *Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered 'yes'.* • *If the distribution of the data (normal or not) is not described, it must be assumed that the estimates used were appropriate and the question should be answered 'yes'.*	
Internal validity – confounding (selection bias) – N/A	

Appendix 3: Ethical Approval "Test-Retest Reliability of TMS Measures of the Corticospinal Pathway in Neurologically Intact Adults of all Ages"

Faculty of Medicine and Health Sciences Research Ethics Committee

University of East Anglia

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Web: www.uea.ac.uk/researchandenterprise

6th February 2014

Dear Kathryn

Project title: The reliability of brain-muscle connectivity across the lifespan
Reference: 2013/2014 - 20

The amendments to your above proposal have been considered by the Chair of the Faculty Research Ethics Committee and we can confirm that your proposal has been approved.

Please could you ensure that any further amendments to either the protocol or documents submitted are notified to us in advance and also that any adverse events which occur during your project are reported to the Committee. Please could you also arrange to send us a report once your project is completed.

The Committee would like to wish you good luck with your project.

Yours sincerely,

Yvonne Kirkham
Project Officer

cc supervisor by email

Appendix 4: Ethical Approval of Amendments "Test-Retest Reliability of TMS Measures of the Corticospinal Pathway in Neurologically Intact Adults of all Ages"

Faculty of Medicine and Health Sciences Research Ethics Committee

University of East Anglia

Kathryn Collins
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20 June 2014

Dear Kathryn,

Project title: The reliability of brain-muscle connectivity across the lifespan
Reference: 2013/2014 - 20

Thank you for your e-mail dated 04.06.14 notifying us of the amendments you would like to make to your above proposal. These have been considered by the Chair of the Faculty Research Ethics Committee and we can now confirm that your amendments have been approved.

Please can you ensure that any further amendments to either the protocol or documents submitted are notified to us in advance, and also that any adverse events which occur during your project are reported to the Committee.

Please can you also arrange to send us a report once your project is completed.

Yours sincerely,

Mark Wilkinson
Chair
FMH Ethics Committee

cc Niamh Kennedy

Appendix 5: Consent Form

Participant Number	Initials	Date of Visit
_____	_____	_____
		D D M M Y Y Y Y

Study Title: The reliability of brain-muscle connectivity across the lifespan

University of East Anglia

Consent form **Please Initial the box**

1. I have read and understand the participant information sheet, and had the opportunity to ask questions, have my questions answered to my satisfaction, and had time to consider my participation in the study. ☐
2. I understand that my participation is voluntary and I do not have to take part. I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected. ☐
3. I understand that I will be attending 2 sessions at the Movement Laboratory. I will have measurements of cortical and muscle activity taken, complete a questionnaire and a dexterity task. ☐
4. I understand that all data collected will be anonymous and kept confidential. ☐
5. I confirm that I have completed a medical history screening and do not have any implanted metal that would preclude me from the study. ☐
6. I agree to take part in the study. ☐

Print Name (participant) _____ Date _____

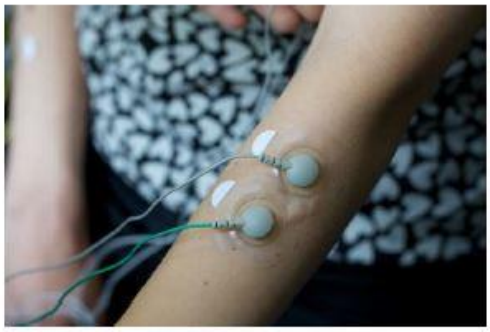
Signed Name (participant) _____ Date _____

Print Name (researcher) _____ Date _____

Signed Name (researcher) _____ Date _____

The reliability of brain-muscle connectivity across the lifespan, Consent Form version 2.0, 18 December 2013

Appendix 6: Recruitment Poster



Faculty of Medicine and Health,
University of East Anglia

We need your help in a research project to investigate how the brain connects to the muscle to produce skilled movement!

Imagine not being able to pick up a cup of coffee, do up a zip or sign a letter. These are the problems faced everyday by people who have survived a stroke. Our research programme is seeking better therapies for people after stroke. This present study will find out if a highly specialized measurement tool, called transcranial magnetic stimulation (TMS), is able to measure brain-muscle connectivity in a consistent manner. If the answer is yes then we will be able to use TMS to provide early indications of whether specific therapies will work for individuals after stroke. In this way it is envisaged the right therapy will be given to the right people early after stroke and recovery will be enhanced. The first step is to find whether TMS is the appropriate measurement tool.

If you are aged at least 18 years, are healthy and would like to assist

Please Contact Katey Collins
Telephone: 01603 593093
Email: kathryn.collins@uea.ac.uk

Katey Collins 01603 593093 OR Kathryn.Collins@uea.ac.uk	Katey Collins 01603 593093 OR Kathryn.Collins@uea.ac.uk	Katey Collins 01603 593093 OR Kathryn.Collins@uea.ac.uk	Katey Collins 01603 593093 OR Kathryn.Collins@uea.ac.uk	Katey Collins 01603 593093 OR Kathryn.Collins@uea.ac.uk	Katey Collins 01603 593093 OR Kathryn.Collins@uea.ac.uk	Katey Collins 01603 593093 OR Kathryn.Collins@uea.ac.uk

Appendix 7: Participant Information Sheet

Participant Information Sheet

Participant Information Sheet version 3.0 associated with protocol version 3.0 dated 30 April 2014

Participant Information Sheet

Title of Project: The reliability of brain-muscle-connectivity across the lifespan

Researchers: Kathryn Collins, PhD Student

Professor Valerie Pomeroy

Dr. Niamh Kennedy

Dr. Allan Clark

We would like to invite you to take part in this project. Before you decide we would like you understand why the research is being done and what it would involve. We will go through the information sheet with you and answer any questions you may have. This will take about 10 minutes.

You may discuss the research with others and take time to decide if you would like to take part.

Taking part in the research is completely voluntary.

- **What is the purpose of the project?**

  This project is part of a PhD thesis, looking at the connection between your brain and your muscles. The brain-muscle connection provides smooth arm movement which allows you to complete everyday tasks such as eating and dressing. When we learn new activities our brain form new connections, these connections can be measured though the assessment of the brain-muscle connection. .

The brain-muscle connection can be measured using Transcranial Magnetic Stimulation (TMS). TMS is a painless brain stimulation technique; it involves, a magnetic impulse given over the scalp, the response is measured at the muscles

of your arm and hand. The muscle response is measured by placing electrodes on the skin over the muscles.

It is important that any measurement tool must be reliable. Reliability is a measure of day to day change or stability of a measurement. The reliability of TMS has been studied in the healthy population of mainly younger adults demonstrating good results. Recent research has found many factors may influence the brain-muscle connection for example aging, time of day, exercise, caffeine, and smoking. As age and other factors may influence the brain-muscle connection the results in the younger adults may not be relevant to individuals of all ages.

By looking at the reliability within individuals of all ages it can provide knowledge on how reliability changes with age or the influence of the other factors. The results will provide a comparison to those older adults who have had a stroke. This project aims to determine the reliability of brain-muscle connection measurement across the lifespan, and determine if the brain muscle connection is influenced by factors such as age, physical activity, caffeine, & smoking.

- **Why have I been invited?**

    - You have been invited because you are a healthy adult who is at least 18 years of age and has expressed interest in the research. If you decide to take part you will be one of 51 participants in the study.

- **Do I have to take part?**

    - It is up to you to decide to take part. Participation is voluntary and you do not have to participate. We will describe the assessments and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw from this research at any time without giving a reason.

- **What will happen to me if I take part?**

- Once you have shown interest in the project you will be contacted by the researcher. We will go through the participant information sheet and answer any questions you may have. If you would like to continue and are suitable for the project then we will arrange a convenient time for you to attend the Movement Laboratory in the Medical School, University of East Anglia, UEA.

- Please see the map at the end of this participant information sheet, or you can find a map at www.uea.ac.uk . The Medical School building has been circled (K, 17). If you plan to drive you will be given a permit to park in the car park behind the Medical School building.
- This project will require you to **attend 2 sessions** between 5 and 7 days apart at the Movement Laboratory within the Medical School Building at UEA. Each session will last approximately 60 minutes.
- When you arrive at the lab we will review the procedures and equipment and answer any questions you may have. If you are suitable and happy to proceed with the experiment we will obtain written informed consent before initiating the experiment.

- **Am I suitable to take part in the experiment?**
  - **I am a healthy (no known neurological condition) adult at least 18 years of age.**
  - The following questions are to determine if you are suitable to participate in TMS.
  - **If you have any implanted metal you will not be able to participate in this project.**

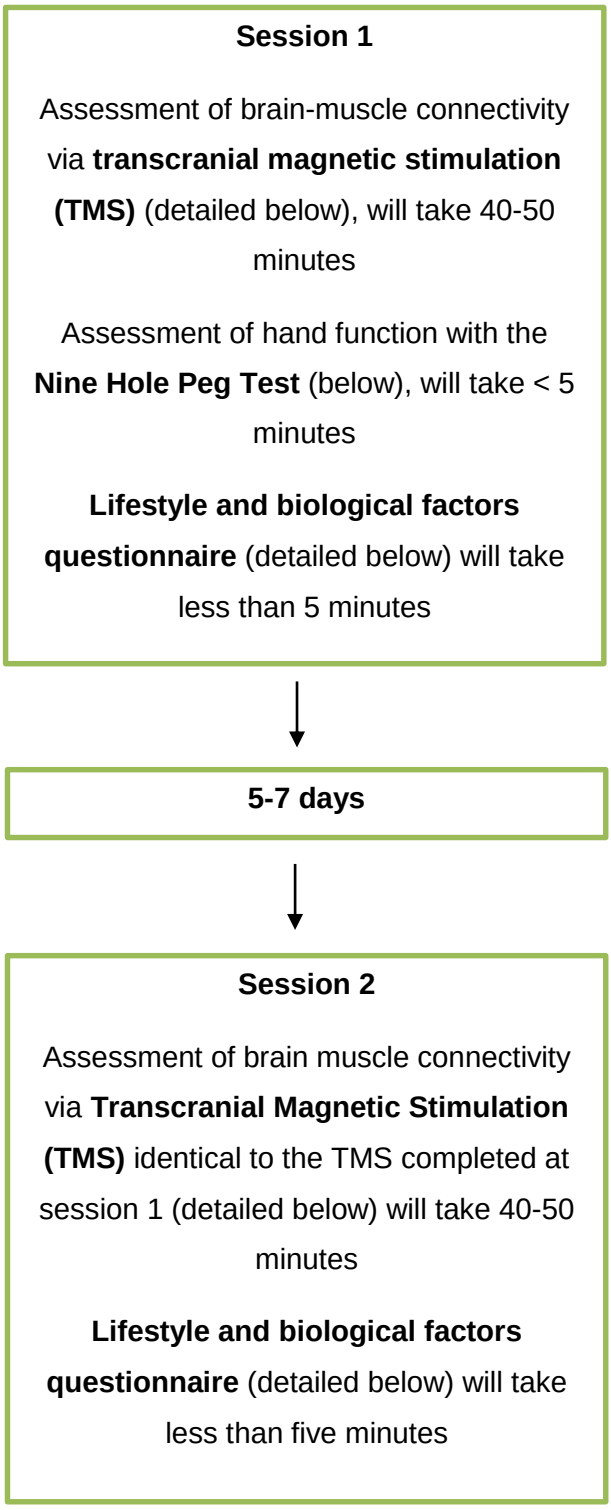
Medical Screening Questions

1. Do you have a heart pacemaker, artificial heart valves, pacing wires or defibrillator?
2. Do you have any implanted devices (e.g. programmable hydrocephalus shunt; nerve stimulator; cochlear implant; aneurysm clip; insulin, drug or infusion pump)?
3. Have you had any surgery to your head (including ears/eyes/brain), neck or spine?
4. Have you ever sustained any injuries involving metal to the eyes or any other part of the body?
5. Have you ever had a fit or blackout, or do you have epilepsy?
6. Are you pregnant?

If you answered yes to any of the above questions you will be asked to not take part in the project. If you are unsure or have any questions please ask the researcher.

• **What will happen during the experiment?**

Flow Chart of Sessions



Transcranial Magnetic Stimulation- timing 40-50 minutes

- In order to assess brain muscle connectivity we will use Transcranial Magnetic Stimulation, TMS, the response will be measured at the muscle using electrodes (see photo 2)

- Transcranial Magnetic Stimulation is an assessment involving the use of a device for producing pain-free stimulation of the areas of the brain that control movement. In response to this stimulation, muscles of the body generate a natural brief contraction. This muscle activity can be recorded from muscles with electrodes using a method called electromyography (EMG). The examination of the EMG muscle recordings following TMS can provide information on how well signals sent from the brain connect to muscles in the arm and hand.

Photo 1

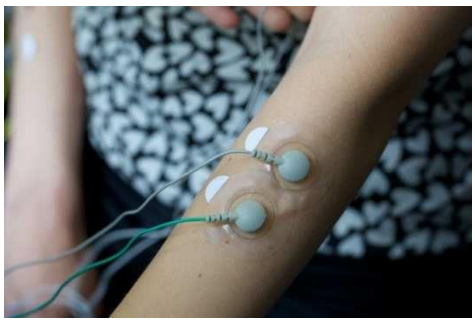
A participant receiving TMS

- Throughout the experiment you will be seated comfortably in chair.

- The first step involves cleansing the skin over the muscles of your arm, forearm and hand. This is done with a recommended gel, wiping it, and letting it dry.

- Once the skin is dry adhesive electrodes will be placed on the skin over the muscles of your arm, forearm and hand. These electrodes send signals via wires to the computer about your muscle activity during TMS. You will not feel anything from the electrodes during the experiment.

Photo 2



Electrode placement on the arm

- You will then be asked to make three maximum effort contractions of a muscle in your arm, forearm, and hand. This contraction will be used to determine the strength of the contraction that will be used throughout the assessment.

- Next we will use TMS to investigate the connection between the brain and muscle, and measure the response at your muscle while you maintain a slight muscle contraction. This will be repeated for the muscles of your arm, forearm and hand.
  The stimulation is painless. You can stop stimulation at any time.

Clinical Assessment- timing less than 10 minutes

- Nine Hole Peg Test- timing 5 minutes ○ To assess dexterity (coordination of your fingers) you will complete the Nine Hole Peg Test. This involves taking pegs one at a time from a container and placing them into holes, then returning the pegs one at a time to the container. This will be completed with each hand.

Photo 3

A participant completing the Nine Hole Peg Test

Questionnaire- timing 5 minutes

- Finally, you will be asked to complete a questionnaire about lifestyle and biological factors that previous research has found to influence brain-muscle connectivity. This will take less than 5 minutes; if you need assistance completing the questionnaire the researcher will assist you.

If you require transportation to the Movement Lab at UEA a taxi will be arranged for you at no cost.

- **What are the possible disadvantages and risks of taking part?**

  - The researchers do not anticipate any major disadvantages to taking part in this project.

  - There is a small risk that you may experience discomfort from the stimulation. The stimulation can be stopped at any time. If you would like the experiment to stop tell the researcher and the experiment will end.

- **What will happen if I don't want to carry on with the study?**
  - You may stop the experiment at any time, simply ask the researcher to stop. You do not need to provide a reason.

  - You may withdraw from the study at any time without giving a reason..

- **What are the benefits to taking part in the research?**

  - Your data and information will help us better understand brain-muscle connectivity across the lifespan, and how lifestyle and biological factors may influence the connection.

- **What may prevent me from taking part?**

  - You will complete a medical history screening questionnaire to determine if you are suitable for TMS. If you have implanted metal, a pacemaker, other implanted devices or conditions such as epilepsy it is recommended that you do not have brain stimulation. Individuals with a skin condition such as eczema cannot participate due to the skin preparation used in EMG.

- **Will my participation in the project be kept confidential?**

    - All of the information and data collected will be anonymous and kept confidential.
    - Your name or other identifiable information will not be used on any of the forms.
    - You will be given a unique ID number that only the researchers can match with your name. The data will be stored in a locked cabinet in which only the researchers have access to. All data from the muscle recordings will be kept securely on a laptop with a passcode that only the researchers have access to. The only time confidentiality may be broken is if you tell us something that may cause us concern for your welfare. According to UEA Faculty of Medicine and Health guidelines, data will be stored securely for five years.

- **What will happen to the results of the project?**

    - This project is part of a PhD thesis and will be written up by the PhD student. The results may be published in academic journals and presented at professional conferences. All data will remain confidential and individuals will not be identifiable if the results are published. You can receive feedback on the projects findings by request.

- **What if any issues arise during my involvement in the project that causes me concern?**

    - If you have a concern or issue during the assessments you should ask to speak to your researcher who will answer any questions or find someone who can.
    - You may also contact Nick Leavey; his contact details are:
      Nick Leavey, School of Rehabilitation Sciences

      University of East Anglia

      Norwich Research Park

      Norwich

      NR4 7TJ

      Phone: 01603 591263

      Email: n.leavey@uea.ac.uk

Participation in this research is voluntary, and completely up to you; you may withdraw at any time without giving a reason.

Thank you for taking the time to read this.

If you have any further questions please contact:

Kathryn Collins

School of Rehabilitation Sciences

University of East Anglia

Phone: 01603 593093

Email: Kathryn.collins@uea.ac.uk

Appendix 8: Health Screening Questionnaire

Medical Screening Questionnaire

Please answer the following questions. When you are finished the researcher will go over the answers with you.

Thank you.

Question	Yes	No
1. Do you have a heart pacemaker, artificial heart valves, pacing wires or defibrillator?		
2. Do you have any implanted devices (e.g. programmable hydrocephalus shunt; nerve stimulator; cochlear implant; aneurysm clip; insulin, drug or infusion pump)?		
3. Have you had any surgery to your head (including ears/eyes/brain), neck or spine?		
4. Have you ever sustained any injuries involving metal to the eyes or any other part of the body?		
5. Have you ever had a fit or blackout, or do you have epilepsy?		
6. Have you ever had an MRI?		
7. Are you pregnant?		

Appendix 9: Lifestyle and Environmental Factors Questionnaire

Participant Number	Initials	Date of Visit
|__|__|	|__|__|__|	|__|__|__|__|__|__|__|__| D D M M Y Y Y Y

Lifestyle and Biological Factors Questionnaire

Please take a few minutes to answer the following questions. If you need assistance please ask the researcher.

1. Gender	[ ] Male [ ] Female
2. Age and Date of Birth	_____
3. Handedness	[ ] Right [ ] Left [ ] Ambidextrous
4. Do you participate in regular exercise?	[ ] Yes [ ] No (If no please go to question # 7)
5. How many times a week to you exercise?	_____
6. What type of exercise to you participate in? (for example walking, aerobics, weight training, yoga)	_____ _____
7. Do you take any medications?	[ ] Yes [ ]No (If No please go to question # 9) If Yes please list medications:_____ _____
8) Please list the medications have you taken already today?	_____ _____
9) What is your past or current occupation?	_____
10) Do you drink caffeinated drinks? (for example coffee, tea, cola)	[ ] Yes [ ] No (If no please go to question #12)
11) Did you drink a caffeinated drink today?	[ ] Yes [ ] No
12) Do you smoke cigarettes?	[ ] Yes [ ] No (If no Questionnaire is complete)
13) On average how many cigarettes do you smoke a day?	_____

Appendix 10: Tables of MEP Amplitude Subgroup Analysis

Table 43 - Reliability of Active MEP Amplitude of Dominant Biceps - Resting Conditions

Participant subgroup	% of RMT	ICC (95% CI)	95% LOA	Reliability Category
Whole group n=27	90	-0.056 (0, 0.225)	-1.198 to 1.861	Poor
Women n=17	90	-0.018 (0, 0.351)	-0.867 to 1.197	Poor
Men n=20	90	-0.137, (0, 0.331)	-1.439 to 2.586	Poor
≥ 50 years of age =8	90	0.126, (0, 0.551)	-0.770 to 1.649	Poor
≤ 49 years of age n=29	90	-0.140, (0, 0.229)	-1.253 to 2.170	Poor
Exercisers n=29	90	-0.179, (0, 0.146)	-1.251 to 2.010	Poor
Non-exercisers n=8	90	0.124, (0, 0.710)	-0.504 to 0.616	Poor
Whole group n=36	100	-0.058 (0, 0.218)	-1.9269842 to 2.7274501	Poor
Women n=21	100	0.002, (0, 0.369)	-1.875 to 2.375	Poor
Men n=15	100	-0.155, (0, 0.279)	-1.998 to 3.139	Poor
≥ 50 years of age =11	100	0.251, (0, 0.652)	-1.423 to 2.315	Poor
≤ 49 years of age n=25	100	-0.220, (0, 0.130)	-2.038 to 3.108	Poor
Exercisers n=25	100	-0.204, (0, 0.121)	-2.071 to 3.037	Poor
Non-exercisers n=11	100	0.121, (0, 0.647)	-0.396 to 0.479	Poor
Whole group n=38	110	0.139, (0, 0.403)	-1.833 to 2.357	Poor
Women n=23	110	0.174 (0, 0.514)	-0.938 to 1.477	Poor
Men n=16	110	0.096, (0, 0.500)	-2.765 to 3.268	Poor
≥ 50 years of age =10	110	0.353, (0, 0.711)	-1.023 to 1.852	Poor
≤ 49 years of age n=28	110	0.097, (0, 0.427)	-1.943 to 2.640	Poor
Exercisers n=27	110	0.102, (0, 0.405)	-1.914 to 2.724	Poor
Non-exercisers n=11	110	0.201, (0, 0.708)	-1.180 to 0.935	Poor
Whole group n= 38	120	-0.076, (0, 0.214)	-2.001 to 2.757	Poor
Women n=21	120	-0.131, (0, 0.242)	-1.795 to 2.535	Poor
Men n=17	120	0.129, (0, 0.569)	-2.477 to 3.262	Poor
≥ 50 years of age n=7	120	0.692, (0.212, 0.898)	-0.890 to 0.558	Poor
≤ 49 years of age n=31	120	-0.181, (0, 0.175)	-2.072 to 3.173	Poor
Exercisers n=28	120	-0.107, (0, 0.213)	-2.118 to 3.294	Poor
Non-exercisers n=10	120	0.648, (0.123, 0.897)	-1.087 to 0.908	Poor
Whole group n=22	130	-0.005 (0, 0.336)	-2.188 to 2.115	Poor
Women n= 10	130	-0.119 (0,0.325)	-1.896 to 2.365	Poor
Men n=12	130	0.451, (0, 0.804)	-2.417 to 1.081	Poor
≥ 50 years of age n=4	130	0.791, (0, 0.948)	-0.452 to 0.928	Poor
≤ 49 years of age n=18	130	-0.078, (0, 0.330)	-2.103 to 2.362	Poor
Exercisers n=15	130	-0.196, (0, 0.190)	-2.568 to 2.638	Poor

Participant subgroup	% of RMT	ICC (95% CI)	95% LOA	Reliability Category
Non-exercisers n=7	130	0.550, (0, 0.936)	-1.162 to 0.823	Poor

Table 44 - Reliability of Active MEP Amplitude of Dominant Biceps - Active Conditions 20% MVC

Participant subgroup	% of AMT	ICC (95% CI)	95% LOA	Reliability Category
Whole group n=51	100	0.426, (0.173, 0.626)	-1.606 to 1.428	Poor
Women n= 30	100	0.578 (0.283, 0.774)	-1.917 to 1.746	Poor
Men n=21	100	0.237, (-0.225, 0.604)	-1.148 to 0.960	Poor
≥ 50 years of age n=17	100	0.196, (-0.316, 0.606)	-0.997 to 0.964	Poor
≤ 49 years of age n=34	100	0.405, (0.079, 0.654)	-1.701 to 1.543	Poor
Exercisers n=40	100	0.444, (0.158, 0.661)	-1.579 to 1.493	Poor
Non-exercisers n=11	100	0.233, (-0.471, 0.724)	-1.714 to 1.236	Poor
Whole group n= 51	110	0.465 (0.223, 0.654)	-2.168 to 1.533	Poor
Women n=30	110	0.559 (0.234, 0.767)	-2.441 to 1.803	Poor
Men n=21	110	0.320, (-0.123, 0.655)	-1.817 to 1.187	Poor
≥ 50 years of age n=17	110	0.392, (-0.083, 0.720)	-1.027 to 0.732	Poor
≤ 49 years of age n=34	110	0.426, (0.115, 0.664)	-2.304 to 1.648	Poor
Exercisers n=40	110	0.443, (0.165, 0.658)	-1.919 to 1.559	Poor
Non-exercisers n=11	110	0.564, (-0.031, 0.863)	-2.759 to 1.229	Poor
Whole group n= 51	120	0.453, (0.209, 0.645)	-2.771 to 1.982	Poor
Women n=30	120	0.531 (0.214, 0.746)	-3.073 to 2.312	Poor
Men n=21	120	0.363, (-0.066, 0.680)	-2.396 to 1.573	Poor
≥ 50 years of age n=17	120	0.463, (0.008, 0.759)	-2.187 to 1.234	Poor
≤ 49 years of age n=34	120	0.425, (0.115, 0.664)	-2.933 to 2.195	Poor
Exercisers n=40	120	0.432, (0.152, 0.650)	-2.649 to 2.151	Poor
Non-exercisers n=11	120	0.525, (-0.021, 0.841)	-2.989 to 1.257	Poor
Whole group n=51	130	0.499, (0.265, 0.678)	-3.091 to 2.289	Poor
Women n= 30	130	0.573 (0.263, 0.773)	-3.368 to 2.631	Poor
Men n=21	130	0.422, (-0.005, 0.718)	-2.763 to 1.882	Poor
≥ 50 years of age n=17	130	0.591, (0.179, 0.825)	-2.370 to 1.347	Poor
≤ 49 years of age n=34	130	0.465, (0.161, 0.691)	-3.283 to 2.549	Poor
Exercisers n=40	130	0.497, (0.229, 0.697)	-2.748 to 2.387	Poor
Non-exercisers n=11	130	0.384, (-0.118, 0.769)	-3.799 to 1.563	Poor

Table 45 - Reliability of Average MEP Amplitude of Non-Dominant Biceps - Active Conditions

Participant subgroup	% of AMT	ICC (95% CI)	95% LOA	Reliability Category
Whole group n=51	100	0.539, (0.314, 0.707)	-1.599 to 1.876	Poor
Women n= 30	100	0.353, (-0.011, 0.632)	-2.013 to 2.381	Poor
Men n=21	100	0.629, (0.292, 0.830)	-0.874 to 1.039	Poor
≥ 50 years of age n=17	100	0.419, (-0.013, 0.728)	-1.027 to 0.695	Poor
≤ 49 years of age n=34	100	0.577, (0.293, 0.766)	-1.667 to 2.131	Poor
Exercisers n=40	100	0.573, (0.320, 0.749)	-1.748 to 2.022	Poor
Non-exercisers n=11	100	0.227, (-0.329, 0.698)	-1.060 to 1.348	Poor
Whole group n=51	110	0.526, (0.299, 0.698)	-2.067 to 2.488	Poor
Women n= 30	110	0.227, (-0.152, 0.542)	-2.524 to 3.076	Poor
Men n=21	110	0.682, (0.361, 0.858)	-1.326 to 1.587	Poor
≥ 50 years of age n=17	110	0.337, (-0.091, 0.676)	-1.136 to 0.786	Poor
≤ 49 years of age n=34	110	0.568, (0.282, 0.761)	-2.184 to 2.842	Poor
Exercisers n=40	110	0.560, (0.304, 0.740)	-2.237 to 2.761	Poor
Non-exercisers n=11	110	0.112, (-0.432, 0.632)	-1.318 to 1.407	Poor
Whole group n=51	120	0.626, (0.428, 0.767)	-2.141 to 2.665	Poor
Women n= 30	120	0.425, (0.081, 0.679)	-2.552 to 3.004	Poor
Men n=21	120	0.766, (0.510, 0.898)	-1.602 to 2.215	Poor
≥ 50 years of age n=17	120	0.483, (0.059, 0.766)	-1.001 to 0.908	Poor
≤ 49 years of age n=34	120	0.649, (0.400, 0.809)	-2.323 to 3.036	Poor
Exercisers n=40	120	0.657, (0.438, 0.802)	-2.277 to 2.855	Poor
Non-exercisers n=11	120	0.254, (-0.239, 0.700)	-1.688 to 2.038	Poor
Whole group n=51	130	0.493, (0.258, 0.674)	-3.024 to 3.870	Poor
Women n= 30	130	0.222, (-0.142, 0.534)	-3.512 to 4.241	Poor
Men n=21	130	0.712, (0.420, 0.871)	-2.426 to 3.413	Poor
≥ 50 years of age n=17	130	0.456, (0.036, 0.749)	-2.349 to 2.716	Poor
≤ 49 years of age n=34	130	0.490, (0.185, 0.710)	-3.202 to 4.195	Poor
Exercisers n=40	130	0.463, (0.186, 0.674)	-3.123 to 4.231	Poor
Non-exercisers n=11	130	0.476, (-0.057, 0.818)	-2.503 to 2.494	Poor

Table 46 - Reliability of Average MEP Amplitude of Dominant ECR - Resting Conditions

Participant subgroup	% of RMT	ICC (95% CI)	95% LOA	Reliability Category
Whole group n=42	90	0.477 (0.230, 0.667)	-1.037 to 1.046	Poor
Women n=24	90	0.431 (0.080, 0.686)	-0.863 to 0.929	Poor
Men n=18	90	0.539, (0.169, 0.780)	-1.247 to 1.188	Poor
≥ 50 years of age n=13	90	0.123, (0, 0.570)	0.988 to 0.914	Poor
≤ 49 years of age n=29	90	0.529, (0.227, 0.737)	-1.060 to 1.089	Poor
Exercisers n=33	90	0.523, (0.250, 0.718)	-1.034 to 0.907	Poor
Non-exercisers n=9	90	0.163, (0, 0.682)	-0.987 to 1.382	Poor
Whole group n=47	100	0.343 (0.075, 0.565)	-1.551 to 1.351	Poor
Women n=28	100	0.352 (0, 0.635)	-1.207 to 1.033	Poor
Men n=19	100	0.315, (-0, 0.637)	-1.924 to 1.694	Poor
≥ 50 years of age n=15	100	0.440, (0, 0.753)	-1.673 to 1.472	Poor
≤ 49 years of age n=32	100	0.319, (0, 0.590)	-1.531 to 1.332	Poor
Exercisers n=38	100	0.370, (0.061, 0.613)	-1.127 to 0.891	Poor
Non-exercisers n=9	100	0.288, (0, 0.731)	-2.508 to 2.432	Poor
Whole group n=49	110	0.457 (0.209, 0.650)	-1.814 to 1.571	Poor
Women n=29	110	0.452 (0.103, 0.700)	-1.574 to 1.282	Poor
Men n=20	110	0.510, (0.116, 0.767)	-2.094 to 1.912	Poor
≥ 50 years of age n=16	110	0.447, (-0.033, 0.758)	-0.990 to 1.458	Poor
≤ 49 years of age n=33	110	0.457, (0.140, 0.689)	-1.932 to 1.677	Poor
Exercisers n=38	110	0.497, (0.215, 0.701)	-1.580 to 1.080	Poor
Non-exercisers n=11	110	0.416, (0, 0.788)	-2.130 to 2.683	Poor
Whole group n=49	120	0.505 (0.264, 0.686)	-1.856 to 1.778	Poor
Women n=29	120	0.490 (0.165, 0.721)	-1.301 to 1.175	Poor
Men n=20	120	0.583, (0.193, 0.810)	-2.384 to 2.366	Poor
≥ 50 years of age n=16	120	0.504, (0.035, 0.788)	-1.880 to 1.922	Poor
≤ 49 years of age n=33	120	0.513, (0.210, 0.726)	-2.060 to 1.951	Poor
Exercisers n=38	120	0.487, (0.204, 0.695)	-1.322 to 0.981	Poor
Non-exercisers n=11	120	0.570, (0.043, 0.859)	-2.653 to 3.386	Poor
Whole group =46	130	0.491 (0.248, 0.676)	-1.690 to 1.811	Poor
Women n=28	130	0.549 (0.240, 0.758)	-1.717 to 1.701	Poor
Men n=18	130	0.450, (0.061, 0.728)	-1.678 to 1.995	Poor
≥ 50 years of age n=15	130	0.350, (-0.167, 0.708)	-1.325 to 1.832	Poor
≤ 49 years of age n=31	130	0.545, (0.252, 0.747)	-1.805 to 1.805	Poor
Exercisers n=35	130	0.581, (0.328, 0.756)	-1.537 to 1.291	Poor
Non-exercisers n=11	130	0.367, (-0.272, 0.779)	-1.595 to 2.885	Poor

Table 47 - Reliability of Average MEP Amplitude of Dominant ECR - Active Conditions

Participant subgroup	% of AMT	ICC (95% CI)	95% LOA	Reliability Category
Whole group= 50	100	0.641 (0.445, 0.778)	-3.022 to 3.321	Poor
Women n= 30	100	0.578 (0.282, 0.774)	-3.579 to 3.467	Poor
Men n=20	100	0.808, (0.584, 0.918)	-2.310 to 3.090	Moderate
≥ 50 years of age n=17	100	0.858, (0.664, 0.944)	-2.043 to 3.937	Moderate
≤ 49 years of age n=33	100	0.517, (0.211, 0.729)	-3.197 to 2.993	Poor
Exercisers n=39	100	0.593, (0.351, 0.762)	-1.688 to 2.048	Poor
Non-exercisers n=1	100	0.761, (0.358, 0.928)	-5.694 to 5.798	Poor
Whole group n=50	110	0.747 (0.596, 0.848)	-2.824 to 3.069	Poor
Women n= 30	110	0.709 (0.472, 0.850)	-3.217 to 3.177	Poor
Men n=20	110	0.842, (0.653, 0.933)	-2.363 to 2.943	Moderate
≥ 50 years of age n=17	110	0.938, (0.845, 0.976)	-1.527 to 3.160	Good
≤ 49 years of age n=33	110	0.665, (0.420, 0.820)	-3.103 to 2.910	Poor
Exercisers n=39	110	0.693, (0.491, 0.825)	-1.649 to 2.163	Poor
Non-exercisers n=11	110	0.811, (0.462, 0.945)	-5.343 to 4.736	Poor
Whole group n=50	120	0.759 (0.613, 0.855)	-2.878 to 3.026	Poor
Women n= 30	120	0.733 (0.508, 0.863)	-3.126 to 3.263	Poor
Men n=20	120	0.829, (0.626, 0.927)	-2.631 to 2.791	Moderate
≥ 50 years of age n=17	120	0.820, (0.586, 0.928)	-1.520 to 2.486	Moderate
≤ 49 years of age n=33	120	0.721, (0.505, 0.852)	-3.228 to 3.116	Moderate
Exercisers n=39	120	0.734, (0.550, 0.850)	-2.026 to 2.562	Moderate
Non-exercisers n=11	120	0.765, (0.337, 0.931)	-4.894 to 3.810	Poor
Whole group n=50	130	0.763 (0.618, 0.857)	-2.860 to 2.925	Moderate
Women n= 30	130	0.723 (0.493, 0.858)	-3.273 to 3.094	Poor
Men n=20	130	0.867, (0.700, 0.944)	-2.373 to 2.725	Good
≥ 50 years of age n=17	130	0.826, (0.596, 0.931)	-1.346 to 2.289	Moderate
≤ 49 years of age n=33	130	0.720, (0.502, 0.851)	-3.231 to 3.019	Moderate
Exercisers n=39	130	0.741, (0.559, 0.854)	-1.923 to 2.227	Moderate
Non-exercisers n=11	130	0.765, (0.328, 0.931)	-5.031 to 4.342	Poor

Table 48 - Reliability of Average MEP Amplitude of Non-Dominant ECR - Active Conditions

Participant subgroup	% of RMT	ICC (95% CI)	95% LOA	Reliability Category
Whole group n=51	100	0.510, (0.277, 0.687)	-1.887 to 1.615	Poor
Women n= 30	100	0.642, (0.373, 0.812)	-1.813 to 1.729	Poor
Men n=21	100	0.151, (0, 0.542)	-1.989 to 1.488	Poor
≥ 50 years of age n=17	100	0.461, (0.010, 0.757)	-1.463 to 0.949	Poor
≤ 49 years of age n=34	100	0.523, (0.232, 0.730)	-1.994 to 1.796	Poor
Exercisers n=40	100	0.465, (0.180, 0.677)	-1.640 to 1.502	Poor
Non-exercisers n=11	100	0.629, (0.127, 0.882)	-2.623 to 1.915	Poor
Whole group n= n=51	110	0.507, (0.270, 0.685)	-2.201 to 2.058	Poor
Women n= 30	110	0.543, (0.238, 0.752)	-2.177 to 2.155	Poor
Men n=21	110	0.446, (0.026, 0.731)	-2.269 to 1.977	Poor
≥ 50 years of age n=17	110	0.577, (0.180, 0.816)	-2.315 to 1.651	Poor
≤ 49 years of age n=34	110	0.502, (0.205, 0.717)	-2.164 to 2.180	Poor
Exercisers n=40	110	0.426, (0.132, 0.650)	-1.903 to 1.951	Poor
Non-exercisers n=11	110	0.729, (0.281, 0.918)	-3.073 to 2.304	Poor
Whole group n=51	120	0.556, (0.332, 0.720)	-2.062 to 2.166	Poor
Women n= 30	120	0.639, (0.371, 0.809)	-1.833 to 1.981	Poor
Men n=21	120	0.434, (0.041, 0.719)	-2.359 to 2.411	Poor
≥ 50 years of age n=17	120	0.724, (0.333, 0.893)	-1.921 to 1.618	Poor
≤ 49 years of age n=34	120	0.505, (0.200, 0.721)	-2.100 to 2.330	Poor
Exercisers n=40	120	0.416, (0.123, 0.642)	-1.845 to 2.181	Poor
Non-exercisers n=11	120	0.804, (0.418, 0.943)	-2.671 to 2.024	Poor
Whole group n=51	130	0.475, (0.230, 0.663)	-2.412 to 2.476	Poor
Women n= 30	130	0.532, (0.220, 0.745)	-2.123 to 2.123	Poor
Men n=21	130	0.365, (0, 0.677)	-2.762 to 2.905	Poor
≥ 50 years of age n=17	130	0.627, (0.199, 0.847)	-1.998 to 1.930	Poor
≤ 49 years of age n=34	130	0.437, (0.118, 0.675)	-2.543 to 2.648	Poor
Exercisers n=40	130	0.281, (0, 0.544)	-2.039 to 2.399	Poor
Non-exercisers n=11	130	0.836, (0.497, 0.953)	-3.419 to 2.522	Poor

Table 49 - Reliability of Average MEP Amplitude of Dominant APB - Resting Conditions

Participant subgroup	% of RMT	ICC (95% CI)	95% LOA	Reliability Category
Whole group n=38	90	0.155, (0, 0.420)	-1.948 to 2.170	Poor
Women n= 23	90	0.135, (0, 0.472)	-1.762 to 1.728	Poor
Men n=15	90	0.215, (0, 0.598)	-2.113 to 2.590	Poor
≥ 50 years of age n=14	90	-0.147, (0, 0.363)	-2.555 to 2.356	Poor
≤ 49 years of age n=24	90	0.454, (0.120, 0.694)	-1.740 to 2.112	Poor
Exercisers n=32	90	0.231, (0, 0.512)	-1.925 to 2.061	Poor
Non-exercisers n=6	90	0.298, (0, 0.769)	-2.136 to 2.678	Poor
Whole group n=46	100	0.302, (0.030, 0.535)	-2.144 to 2.695	Poor
Women n= 27	100	0.257, (0, 0.562)	-1.719 to 1.708	Poor
Men n=19	100	0.398, (0, 0.715)	-2.345 to 3.511	Poor
≥ 50 years of age n=16	100	-0.030, (0, 0.450)	-1.766 to 1.563	Poor
≤ 49 years of age n=30	100	0.532, (0.232, 0.741)	-2.193 to 2.981	Poor
Exercisers n=38	100	0.202, (0, 0.481)	-2.316 to 2.700	Poor
Non-exercisers n=8	100	0.381, (0., 0.818)	-1.592 to 2.675	Poor
Whole group n=47	110	0.388, (0.125, 0.601)	-2.347 to 2.777	Poor
Women n=27	110	0.347, (0.001, 0.624)	-2.138 to 2.470	Poor
Men n=20	110	0.438, (0., 0.734)	-2.628 to 3.180	Poor
≥ 50 years of age n=16	110	-0.192, (0, 0.326)	-2.907 to 2.180	Poor
≤ 49 years of age n=31	110	0.569, (0.285, 0.762)	-2.067 to 2.894	Poor
Exercisers n=37	110	0.361, (0.054, 0.606)	-2.436 to 2.747	Poor
Non-exercisers n=10	110	0.041, (0, 0.643)	-2.131 to 2.952	Poor
Whole group n=45	120	0.190, (0, 0.446)	-3.520 to 3.859	Poor
Women n= 27	120	0.086, (0, 0.433)	-3.557 to 2.830	Poor
Men n=18	120	0.394, (0, 0.708)	-3.073 to 4.745	Poor
≥ 50 years of age n=15	120	0.018, (0, 0.488)	-4.021 to 3.022	Poor
≤ 49 years of age n=30	120	0.276, (0, 0.569)	-3.302 to 4.074	Poor
Exercisers n=37	120	0.162, (0, 0.455)	-3.227 to 3.525	Poor
Non-exercisers n=8	120	0.026, (0, 0.615)	-4.602 to 5.084	Poor
Whole group n=40	130	0.427, (0.159, 0.636)	-3.242 to 3.240	Poor
Women n= 24	130	0.354, (0, 0.641)	-3.285 to 2.622	Poor
Men n=16	130	0.537, (0.110, 0.794)	-2.996 to 3.986	Poor
≥ 50 years of age n=13	130	0.716, (0.357, 0.893)	-3.914 to 2.317	Poor
≤ 49 years of age n=27	130	0.301, (0, 0.586)	-2.827 to 3.430	Poor
Exercisers n=33	130	0.432, (0.134, 0.658)	-2.685 to 2.500	Poor
Non-exercisers n=7	130	0.152, (0, 0.723)	-4.925 to 5.656	Poor

Table 50 - Reliability of Average MEP Amplitude of Dominant APB – Active Conditions

Participant subgroup	% of RMT	ICC (95% CI)	95% LOA	Reliability Category
Whole group n=47	100	0.126, (-0.136,0.377)	-2.214 to 2.967	Poor
Women n= 27	100	0.148 (-0.196, 0.469)	-1.860 to 2.410	Poor
Men n=20	100	0.022, (-0.394, 0.437)	-2.598 to 3.602	Poor
≥ 50 years of age n=16	100	-0.007, (-0.426, 0.436)	-1.615 to 2.310	Poor
≤ 49 years of age n=31	100	0.215, (-0.122, 0.512)	-2.412 to 3.184	Poor
Exercisers n=39	100	0.016, (-0.289, 0.320)	-1.741 to 2.185	Poor
Non-exercisers n=8	100	0.360, (-0.192, 0.765)	-3.107 to 4.870	Poor
Whole group n=48	110	0.441, (0.191, 0.638)	-2.783 to 3.092	Poor
Women n= 27	110	0.397 (0.047, 0.660)	-2.808 to 2.697	Poor
Men n=21	110	0.531, (0.130, 0.780)	-2.719 to 3.569	Poor
≥ 50 years of age n=16	110	0.349, (-0.110, 0.691)	-2.203 to 2.167	Poor
≤ 49 years of age n=32	110	0.483, (0.167, 0.708)	-2.955 to 3.379	Poor
Exercisers n=40	110	0.358, (0.051, 0.602)	-2.586 to 2.560	Poor
Non-exercisers n=8	110	0.673, (0.174, 0.899)	-3.156 to 4.737	Poor
Whole group n=49	120	0.325 (0.053, 0.551)	-4.011 to 4.010	Poor
Women n= 28	120	0.381 (0.022, 0.651)	-3.907 to 4.094	Poor
Men n=21	120	0.193, (-0.273, 0.576)	-4.219 to 3.987	Poor
≥ 50 years of age n=16	120	0.101, (-0.347, 0.524)	-3.512 to 2.642	Poor
≤ 49 years of age n=33	120	0.432, (0.113, 0.672)	-4.127 to 4.408	Poor
Exercisers n=40	120	0.304, (-0.011, 0.562)	-3.609 to 3.644	Poor
Non-exercisers n=9	120	0.233, (-0.467, 0.724)	-5.403 to 5.275	Poor
Whole group n=49	130	0.306, (0.034, 0.536)	-4.498 to 4.163	Poor
Women n= 28	130	0.356 (-0.004, 0.633)	4.515 to 4.381	Poor
Men =21	130	0.208, (-0.257, 0.586)	-4.563 to 3.981	Poor
≥ 50 years of age n=16	130	0.245, (-0.252, 0.634)	-4.868 to 3.231	Poor
≤ 49 years of age n=33	130	0.344, (0.011, 0.610)	-4.344 to 4.431	Poor
Exercisers n=40	130	0.218, (-0.103, 0.496)	-4.137 to 4.029	Poor
Non-exercisers n=9	130	0.414, (-0.217, 0.800)	-5.800 to 4.680	Poor

Table 51 - Reliability of Average MEP Amplitude of Non-Dominant APB – Active Conditions

Participant subgroup	% of RMT	ICC (95% CI)	95% LOA	Reliability Category
Whole group n=47	100	0.459 (0.213, 0.652)	-3.179 to 3.787	Poor
Women n= 27	100	0.588 (0.286, 0.783)	-2.994 to 3.970	Poor
Men n=20	100	0.098, (0, 0.504)	-3.427 to 3.614	Poor
≥ 50 years of age n=17	100	0.485, (0.064, 0.766)	-2.896 to 3.545	Poor
≤ 49 years of age n=30	100	0.448, (0.119, 0.688)	-3.312 to 3.907	Poor
Exercisers n=37	100	0.660, (0.441, 0.805)	-2.357 to 2.914	Poor
Non-exercisers n=10	100	-0.096, (0, 0.536)	-5.353 to 6.138	Poor
Whole group n=48	110	0.280 (0.011, 0.513)	-4.452 to 5.581	Poor
Women n= 28	110	0.320,(0, 0.600)	-4.618 to 6.181	Poor
Men n=20	110	0.335, (0, 0.655)	-4.313 to 4.968	Poor
≥ 50 years of age n=16	110	0.419, (0, 0.733)	-4.637 to 5.484	Poor
≤ 49 years of age n=32	110	0.205, (0, 0.510)	-4.470 to 5.677	Poor
Exercisers n=39	110	0.406, (0.118, 0.634)	-4.081 to 5.097	Poor
Non-exercisers n=10	110	0.047, (0, 0.625)	-5.695 to 7.182	Poor
Whole group n=49	120	0.506 (0.272, 0.685)	-3.929 to 5.282	Poor
Women n= 28	120	0.533 (0.113, 0.772)	-4.079 to 4.956	Poor
Men n=21	120	0.529, (0.155, 0.775)	-3.803 to 5.696	Poor
≥ 50 years of age n=17	120	0.750, (0.440, 0.899)	-3.645 to 4.150	Poor
≤ 49 years of age n=32	120	0.375, (0.045, 0.634)	-4.015 to 5.627	Poor
Exercisers n=38	120	0.462, (0.184, 0.674)	-3.948 to 5.341	Poor
Non-exercisers n=11	120	0.605, (0.035, 0.877)	-4.085 to 5.306	Poor
Whole group n=49	130	0.549 (0.324, 0.716)	-4.311 to 5.136	Poor
Women n= 28	130	0.589 (0.281, 0.786)	-4.730 to 4.999	Poor
Men n=21	130	0.489, (0.087, 0.755)	-3.860 to 5.314	Poor
≥ 50 years of age n=17	130	0.829, (0.560, 0.935)	-4.949 to 5.076	Moderate
≤ 49 years of age n=32	130	0.392, (0.050, 0.650)	-4.166 to 5.203	Poor
Exercisers n=39	130	0.495, (0.223, 0.697)	-3.991 to 5.141	Poor
Non-exercisers n=10	130	0.751, (0.290, 0.927)	-5.413 to 5.171	Poor

Appendix 11: Bland Altman Plots of MEP Amplitude

Figure 57 – Bland-Altman Plots for the Dominant Biceps Muscle Average MEP Amplitude during Resting Conditions

A

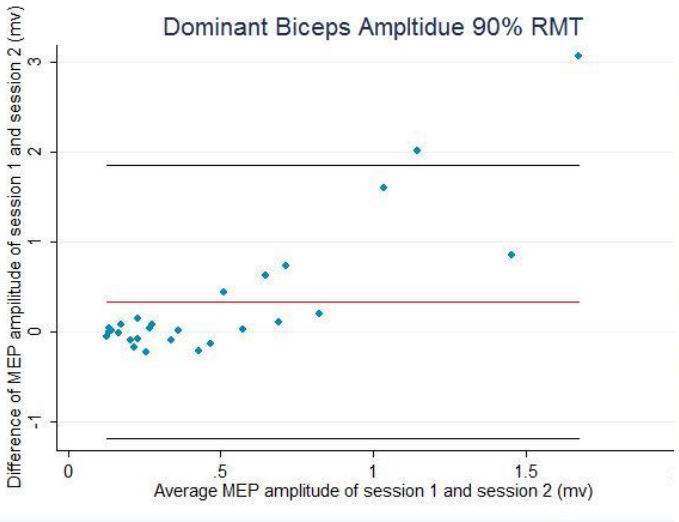


Figure 57A. Bland-Altman plot of the average MEP amplitude for the dominant biceps 90% of RMT n=27

B

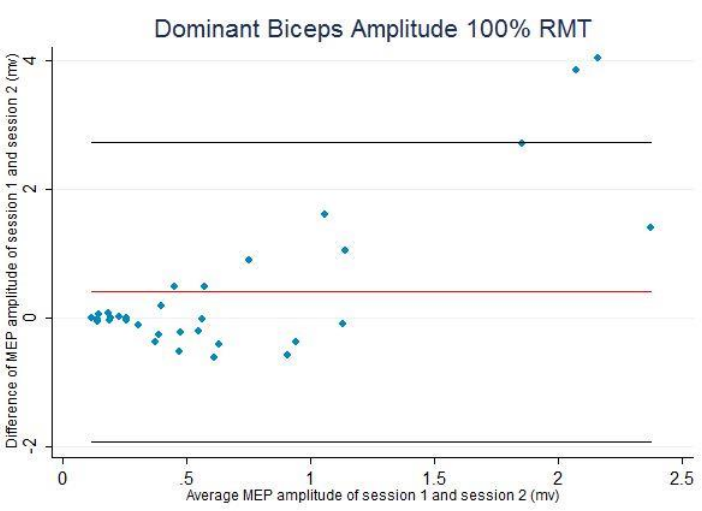


Figure 57B. Bland-Altman plot of the average MEP amplitude for the dominant biceps at 100% RMT n=36

C

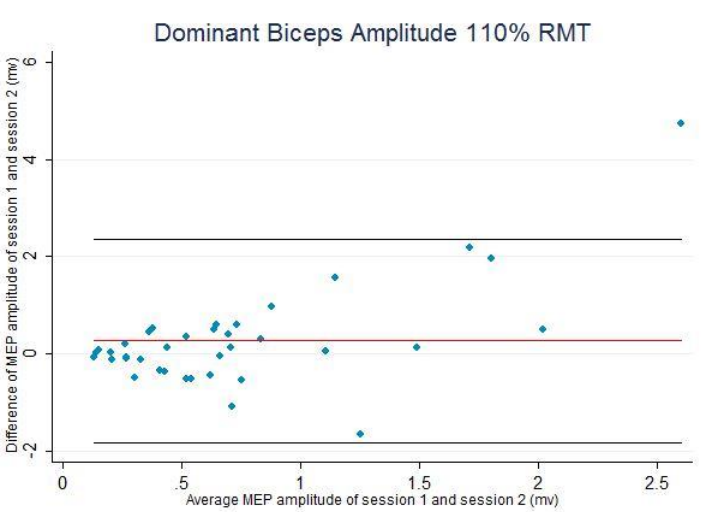


Figure 57C. Bland-Altman plot of the average MEP amplitude of the dominant biceps at 110% RMT n=38

Figure 57A,B,& C - Bland-Altman Plots of the average MEP amplitude of the biceps muscle during resting conditions 90% RMT to 110% RMT. The x axis is the average MEP amplitude measured in mv of session 1 and session 2 plotted against the difference in average MEP amplitude (mv) between session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A demonstrates a potential association between magnitude of MEP and agreement between sessions. Plots B and C demonstrate that with increasing amplitude there is a greater differences in amplitude between sessions. MEP= motor evoked potential, RMT=resting motor threshold

Figure 58 - Bland Altman Plots for the Dominant Biceps Muscle Average MEP Amplitude during Resting Conditions

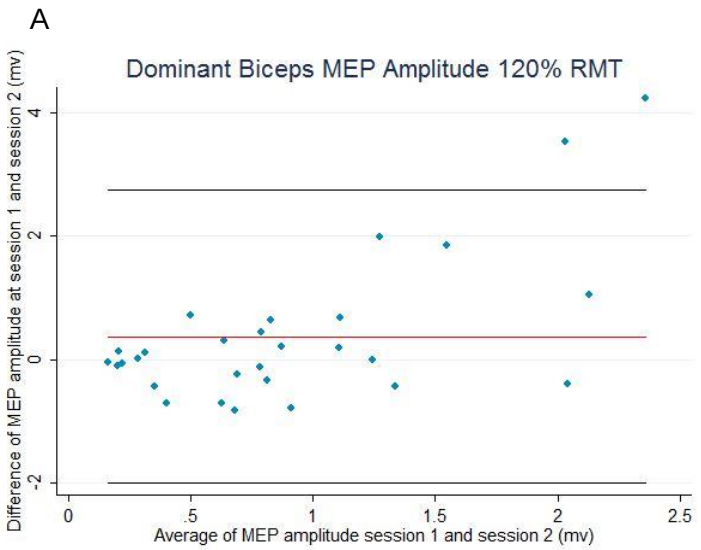


Figure 58A. Bland-Altman plot of the average MEP amplitude of the dominant biceps muscle at 120% RMT n=38

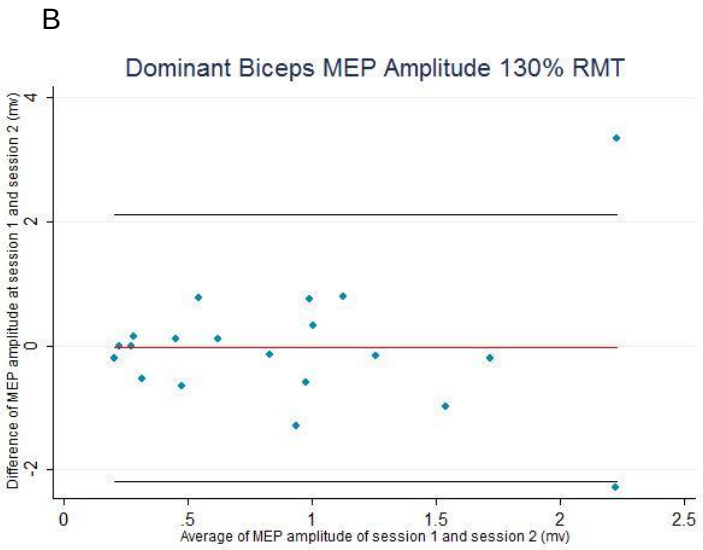


Figure 58B. Bland-Altman plot of the average MEP amplitude of the dominant biceps muscle at 130% RMT n=22

Figure 58A & B - Bland-Altman Plots of the average MEP amplitude of the biceps muscle during resting conditions 120% RMT to 130% RMT. The x axis is the average MEP amplitude measured in mv of session 1 and session 2 plotted against the difference in average MEP amplitude (mv) between session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A and B demonstrate a potential association that as amplitude increases the difference in measurement between sessions increases. MEP= motor evoked potential, RMT=resting motor threshold

Figure 59 - Bland-Altman Plots for the Dominant Biceps Muscle Average MEP Amplitude during Active Conditions

A

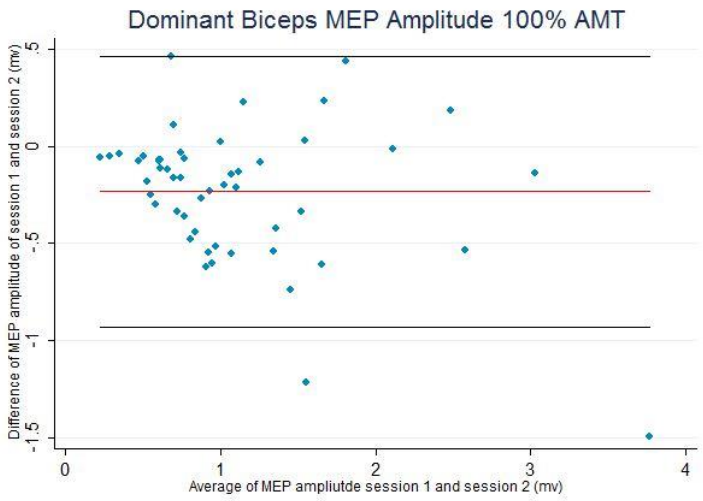


Figure 59 A. Bland-Altman plot of the average MEP amplitude of the dominant biceps muscle at 100% AMT n=51

B

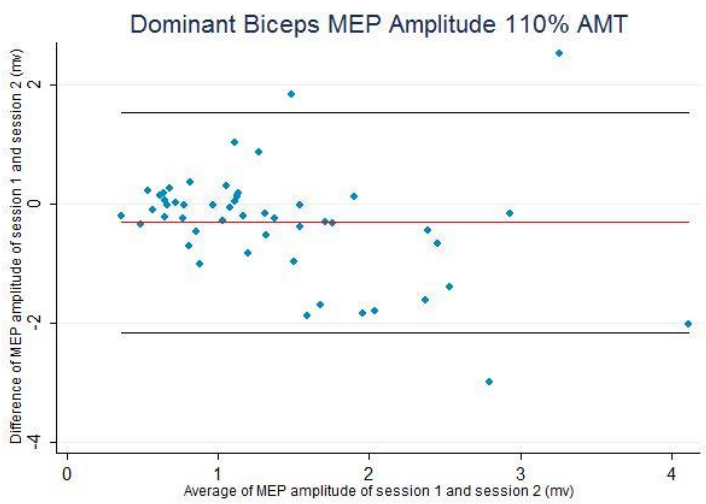


Figure 59 B. Bland-Altman plot of the average MEP amplitude of the dominant biceps muscle at 110% RMT n=51

Figure 59A & B - Bland-Altman Plots of the average MEP amplitude of the biceps muscle during active conditions (20%MVC) at 100% and 110% of AMT. The x axis is the average MEP amplitude measured in mv of session 1 and session 2 plotted against the difference in average MEP amplitude (mv) between session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A and B demonstrate a potential association that as amplitude increases the difference in measurement between sessions increases. MEP= motor evoked potential, AMT=Active motor threshold.

Figure 60 - Bland-Altman Plots for the Dominant Biceps Muscle Average MEP Amplitude during Active Conditions

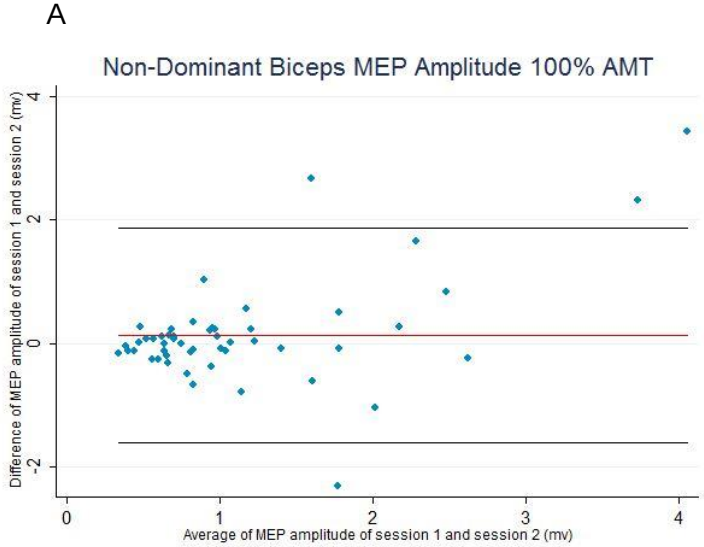


Figure 60A. Bland-Altman plot of the average MEP amplitude of the non-dominant biceps muscle during 100% AMT n=51

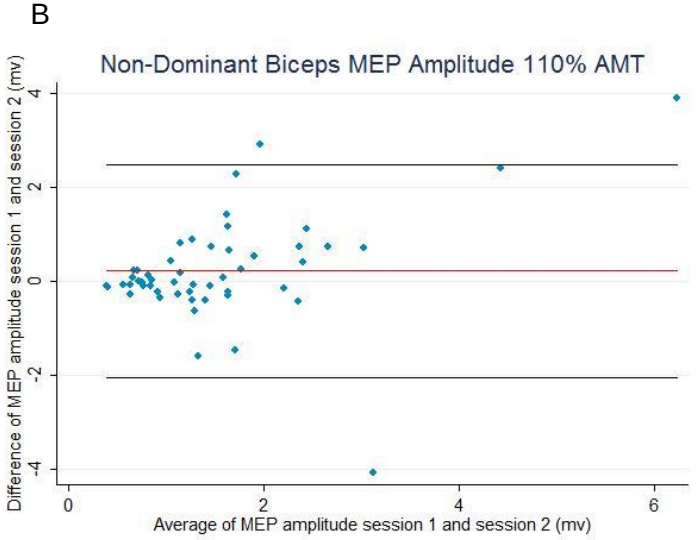


Figure 60B. Bland-Altman plot of the average MEP amplitude of the non-dominant biceps muscle during 110% AMT n=51

Figure 60 A & B - Bland-Altman Plots of the average MEP amplitude of the biceps muscle during active conditions (20%MVC) at 100% and 110% of AMT. The x axis is the average MEP amplitude measured in mv of session 1 and session 2 plotted against the difference in average MEP amplitude (mv) between session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A and B demonstrate a potential association that as amplitude increases the difference in measurement between sessions increases. MEP= motor evoked potential, AMT=Active motor threshold.

Figure 61 - Bland-Altman Plots of the Non-Dominant Biceps Muscle Average MEP Amplitude during Active Conditions

A

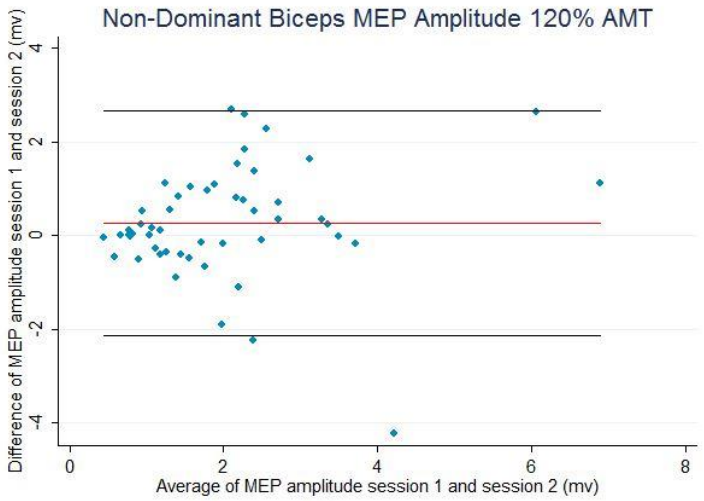


Figure 61 A. Bland-Altman plot of the average MEP amplitude of the non-dominant biceps during 120% AMT n=51

B

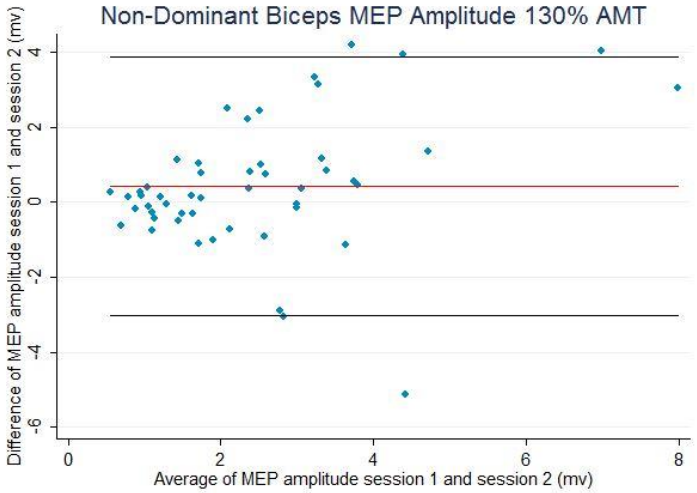


Figure 61 B. Bland-Altman plot of the average MEP amplitude of the non-dominant biceps during 130% AMT n=51

Figure 61 A & B - Bland-Altman Plots of the average MEP amplitude of the biceps muscle during active conditions (20%MVC) at 120% and 130% of AMT. The x axis is the average MEP amplitude measured in mv of session 1 and session 2 plotted against the difference in average MEP amplitude (mv) between session 1 and session 2. The red line is the mean difference in average MEP amplitude between session 1 minus session 2. Plot A and B demonstrate a potential association that as amplitude increases the difference in measurement between sessions increases. MEP= motor evoked potential, AMT=Active motor threshold.

Figure 62 - Bland-Altman Plots of Dominant Extensor Carpi Radialis Average MEP Amplitude during Resting Conditions

A

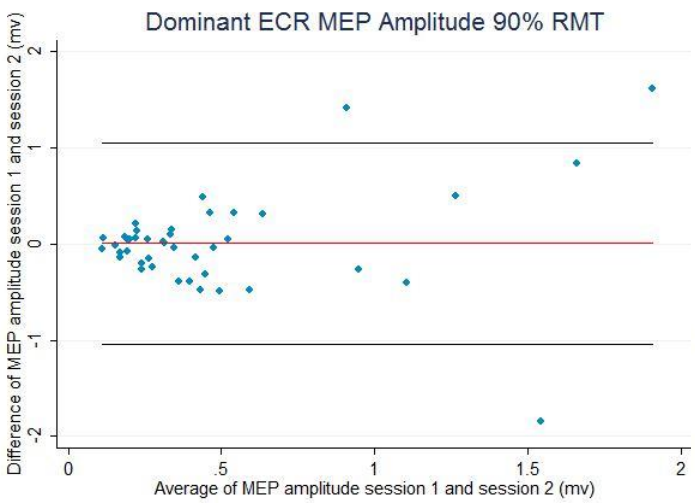


Figure 62 A. Bland-Altman plot of the average MEP amplitude of dominant ECR during 90% RMT n=42

B

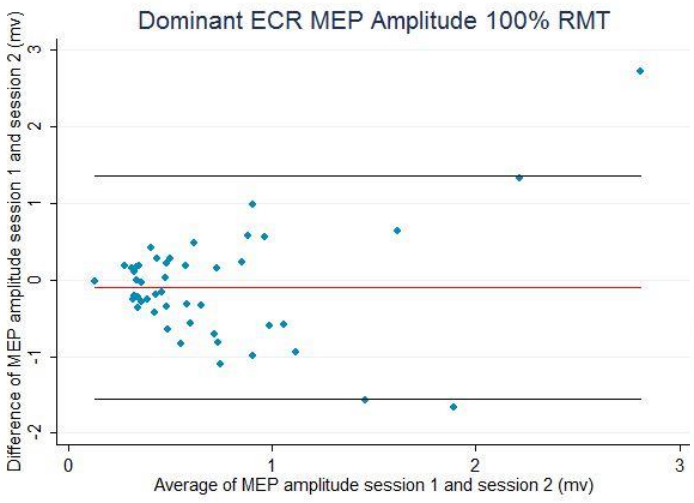


Figure 62 B. Bland-Altman plot of the average MEP amplitude of dominant ECR during 100% RMT n=47

C

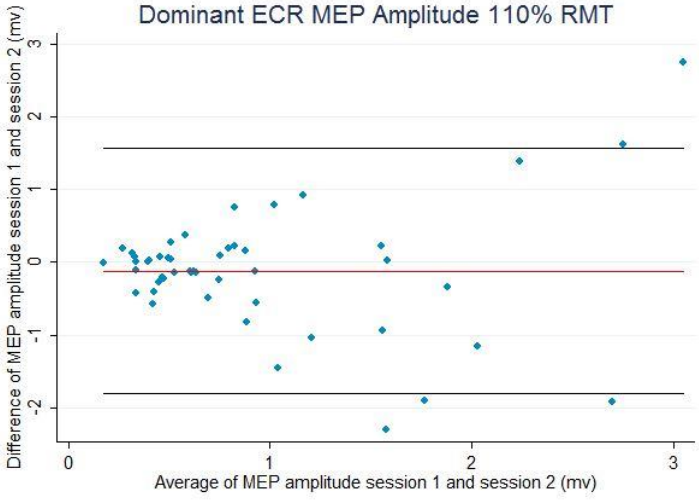


Figure 62 C. Bland-Altman plot of the average MEP amplitude of dominant ECR during 110% RMT n=49

Figure 62 A,B,& C - Bland-Altman Plots of the average MEP amplitude of the biceps muscle during resting conditions 90% RMT to 110% RMT. The x axis is the average MEP amplitude measured in mv of session 1 and session 2 plotted against the difference in average MEP amplitude (mv) between session 1 and session 2. The red line is the mean difference in average MEP amplitude between session 1 minus session 2. Plots A, B, and C demonstrate a potential association that as amplitude increases the difference in measurement between sessions increases. MEP= motor evoked potential, RMT=resting motor threshold, ECR=extensor carpi radialis

Figure 63 - Bland-Altman Plots of the Dominant Extensor Carpi Radilais Average MEP Amplitude during Resting Conditions

A

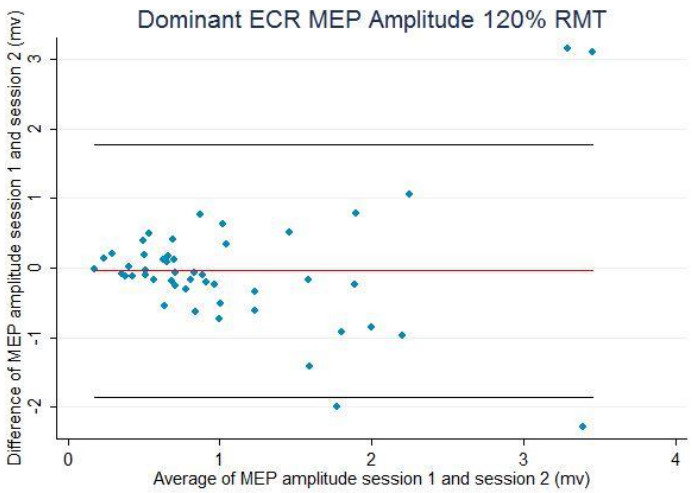


Figure 63 A. Bland-Altman plot of the average MEP amplitude of the dominant ECR during 120% RMT n=49

B

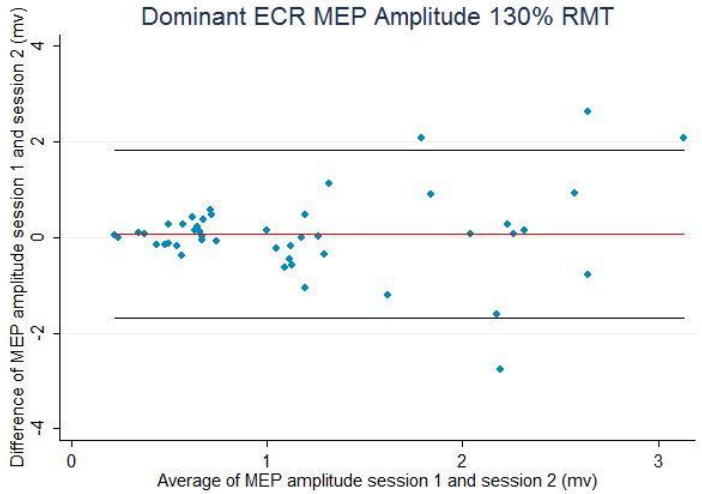


Figure 63 B. Bland-Altman plot of the average MEP amplitude of the dominant ECR during 120% AMT n=46

Figure 63 A & B - Bland-Altman Plots of the average MEP amplitude of the ECR muscle during resting conditions 120%, 130% RMT. The x axis is the average MEP amplitude measured in mv of session 1 and session 2 plotted against the difference in average MEP amplitude (mv) between session 1 and session 2. The red line is the mean difference in average MEP amplitude between session 1 minus session 2. Plots A and B demonstrate a potential association that as amplitude increases the difference in measurement between sessions increases. MEP= motor evoked potential, RMT=resting motor threshold, ECR=extensor carpi radialis

Figure 64 - Bland-Altman Plots of the Non- Dominant Extensor Carpi Radilais Average MEP Amplitude during Active Conditions

A

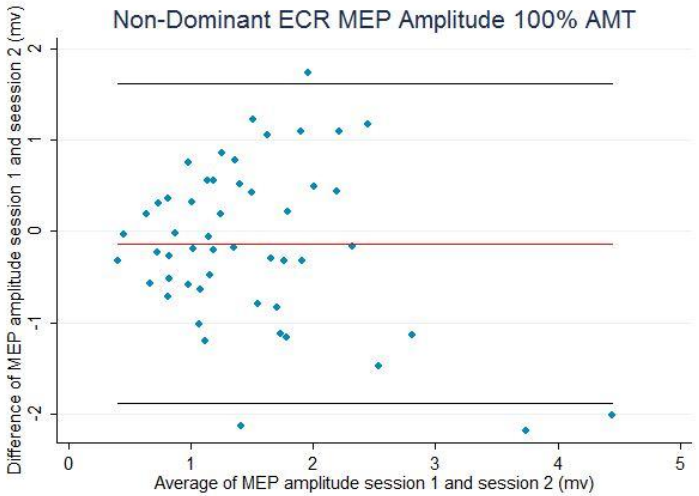


Figure 64 A. Bland-Altman plot of the average MEP amplitude of the non-dominant ECR during 100% AMT n=51

B

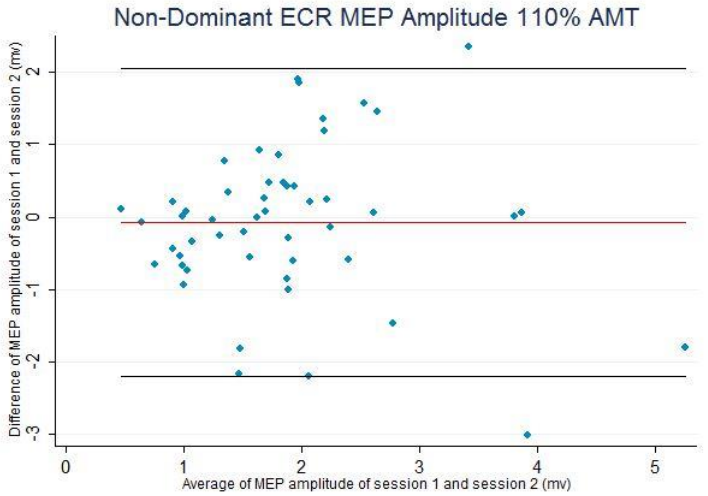


Figure 64 B. Bland-Altman plot of the average MEP amplitude of the non-dominant ECR during 110% AMT n=51

Figure 64 A & B - Bland-Altman Plots of the average MEP amplitude of the ECR muscle during active conditions (20%MVC) at 100% and 110% of AMT. The x axis is the average MEP amplitude measured in mv of session 1 and session 2 plotted against the difference in average MEP amplitude (mv) between session 1 and session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A and B demonstrate a potential association that as amplitude increases the difference in measurement between sessions increases. MEP= motor evoked potential, AMT=Active motor threshold, ECR=extensor carpi radialis

Figure 65 - Bland-Altman Plots of the Non-Dominant Extensor Carpi Radilais Average MEP Amplitude during Active Conditions

A

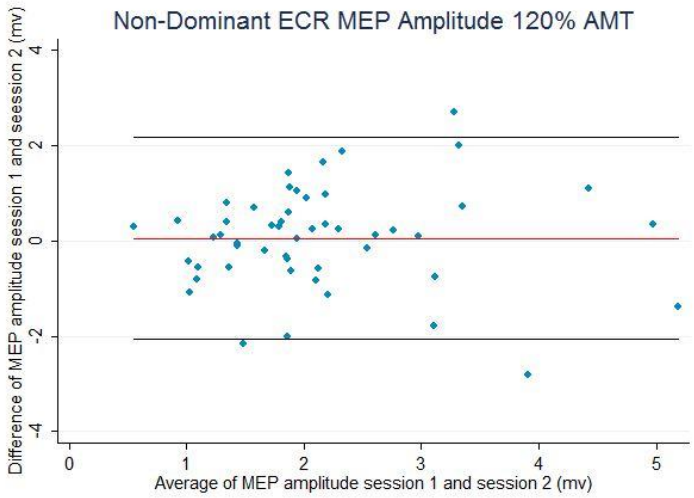


Figure 65 A. Bland-Altman plot of the average MEP amplitude of the non-dominant ECR during 120% AMT n=51

B

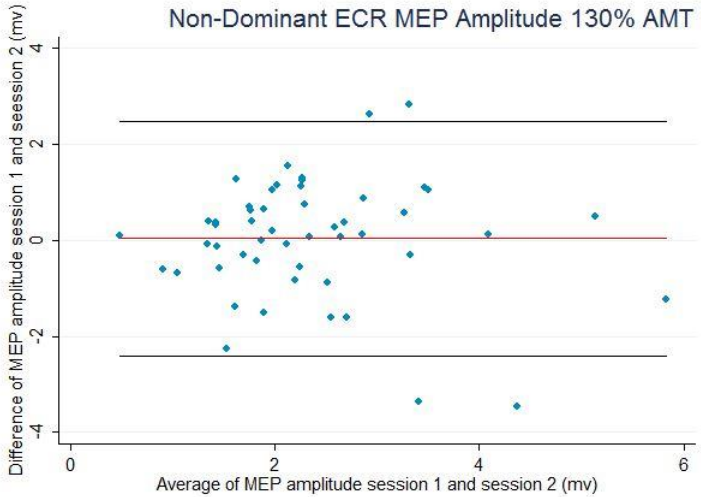


Figure 65 B. Bland-Altman plot of the average MEP amplitude of the non-dominant ECR during 130% AMT n=51

Figure 65 A & B - Bland-Altman Plots of the average MEP amplitude of the ECR muscle during active conditions (20%MVC) at 120% and 130% of AMT. The x axis is the average MEP amplitude measured in mv of session 1 and session 2 plotted against the difference in average MEP amplitude (mv) between session 1 and session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A and B demonstrate a potential association that as amplitude increases the difference in measurement between sessions increases MEP= motor evoked potential, AMT=Active motor threshold, ECR=extensor carpi radialis.

Figure 66 - Bland-Altman Plots of the Dominant Abductor Pollicis Brevis Average MEP Amplitude during Resting Conditions

A

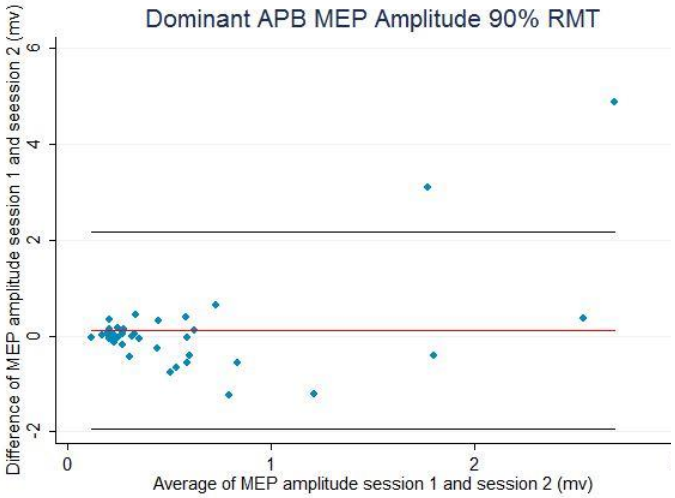


Figure 66 A. Bland-Altman plot of the average MEP amplitude of dominant APB during 90% RMT n=38

B

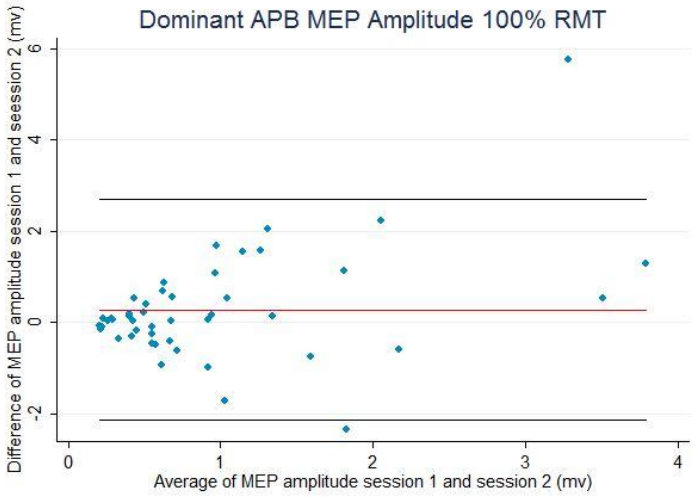


Figure 66 B. Bland-Altman plot of the average MEP amplitude of dominant APB during 100% RMT n=46

C

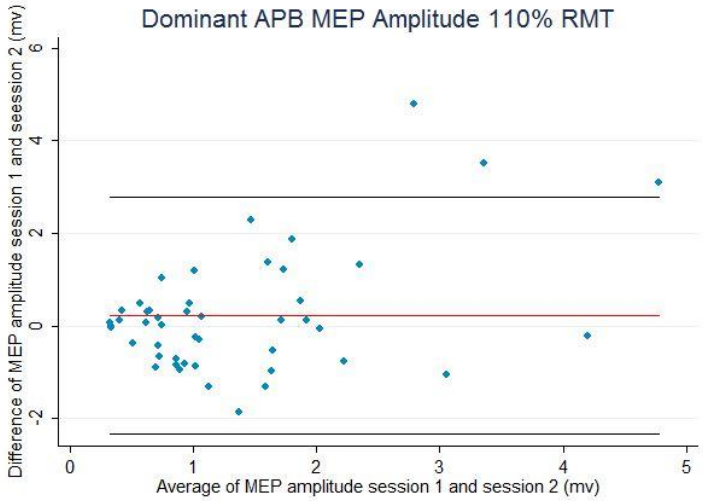


Figure 66 C. Bland-Altman plot of the average MEP amplitude of dominant APB during 110% RMT n=47

Figure 66 A,B,& C - Bland-Altman Plots of the average MEP amplitude of the APB muscle during resting condition 90%, 100%, 110% RMT. The x axis is the average MEP amplitude measured in mv of session 1 and session 2 plotted against the difference in average MEP amplitude (mv) between session 1 and session 2. The red line is the mean difference in average MEP amplitude between session 1 minus session 2. Plots A and B demonstrate a potential association that as amplitude increases the difference in measurement between sessions increases MEP= motor evoked potential, RMT=resting motor threshold, APB=abductor pollicis brevis

Figure 67 - Bland-Altman Plots of the Dominant Abductor Pollicis Brevis Average MEP Amplitude during Resting Conditions

A

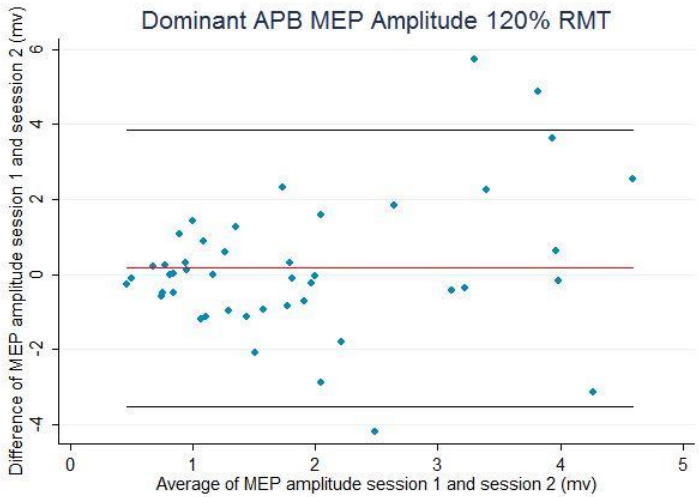


Figure 67A. Bland-Altman plot of the average MEP

B

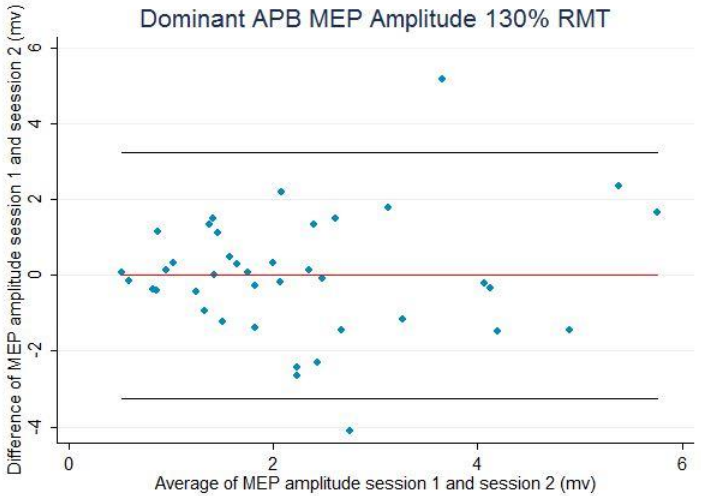


Figure 67B. Bland-Altman plot of the average MEP amplitude of the dominant APB during 130%

Figure 67 A & B - Bland-Altman Plots of the average MEP amplitude of the APB muscle during resting motor threshold 120%, 130%, RMT. The x axis is the average MEP amplitude measured in mv of session 1 and session 2 plotted against the difference in average MEP amplitude (mv) between session 1 and session 2. The red line is the mean difference in average MEP amplitude between session 1 minus session 2. Plots A and B demonstrate a potential association that as amplitude increases the difference in measurement between sessions increases. MEP= motor evoked potential, RMT=resting motor threshold, APB=abductor pollicis brevis

Figure 68 - Bland-Altman Plots of the Dominant Abductor Pollicis Brevis Average MEP Amplitude during Active Conditions

A

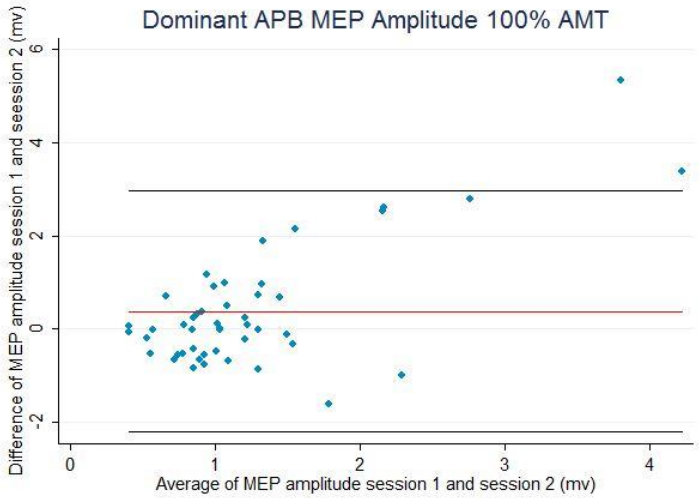


Figure 68A. Bland-Altman plot of the average MEP

B

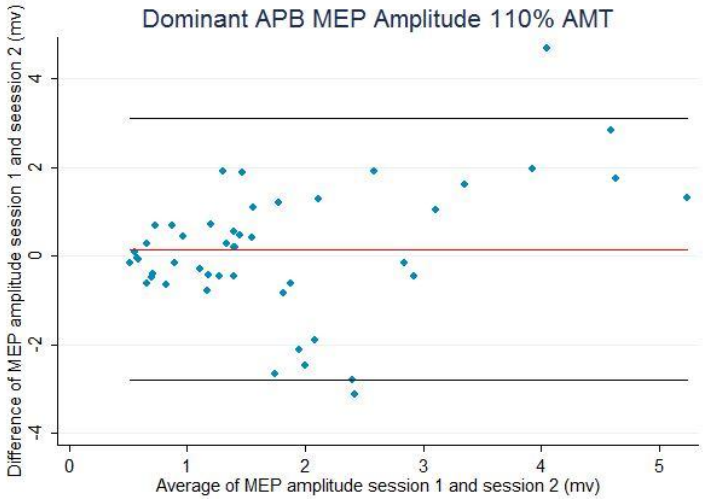


Figure 68 B. Bland-Altman plot of the average MEP amplitude of the dominant APB during 110%

Figure 68A & B - Bland-Altman Plots of the average MEP amplitude of the APB muscle during active conditions (20%MVC) at 100% and 110% of AMT. The x axis is the average MEP amplitude measured in mv of session 1 and session 2 plotted against the difference in average MEP amplitude (mv) between session 1 and session 2. The red line is the mean difference in average MEP amplitude between session 1 minus session 2. Plots A and B demonstrate a potential association that as amplitude increases the difference in measurement between sessions increases MEP= motor evoked potential, AMT=Active motor threshold, APB=abductor pollics brevis

Figure 69 - Bland-Altman Plots of the Dominant Abductor Pollicis Brevis Average MEP Amplitude during Active Conditions

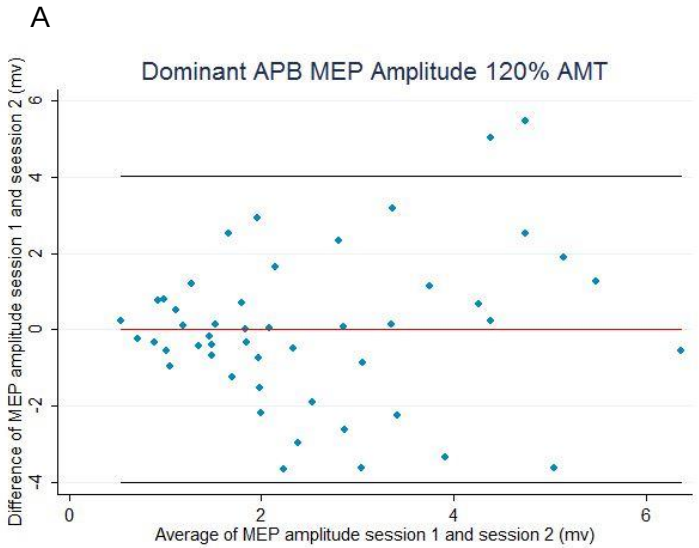


Figure 69 A. Bland-Altman plot of the average MEP amplitude of the dominant APB during 120% AMT n=49

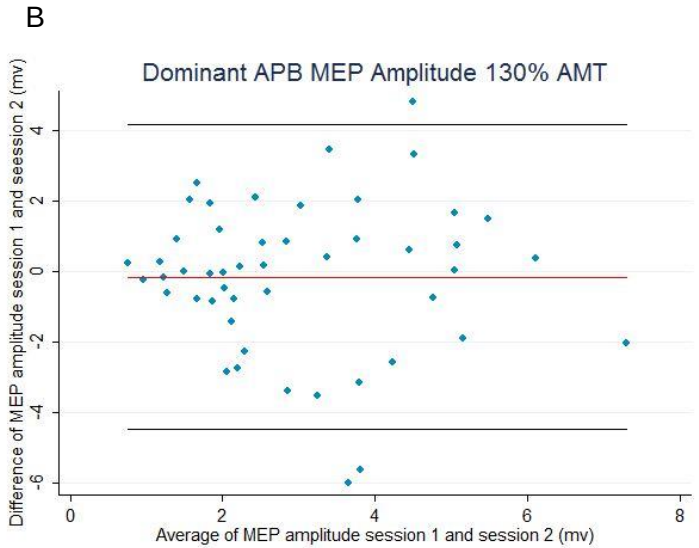


Figure 69 B. Bland-Altman plot of the average MEP amplitude of dominant APB during 130% AMT, n=49

Figure 69 A & B - Bland-Altman Plots of the average MEP amplitude of the APB muscle during active conditions (20%MVC) at 120% and 130% of AMT. The x axis is the average MEP amplitude measured in mv of session 1 and session 2 plotted against the difference in average MEP amplitude (mv) between session 1 and session 2. The red line is the mean difference in average MEP amplitude between session 1 minus session 2. Plots A and B demonstrate a potential association that as amplitude increases the difference in measurement between sessions increases MEP= motor evoked potential, AMT=Active motor threshold, APB=abductor pollicis brevis

Figure 70 - Bland-Altman Plots of the Non-Dominant Abductor Pollics Brevis Average MEP Amplitude during Active Conditions

A

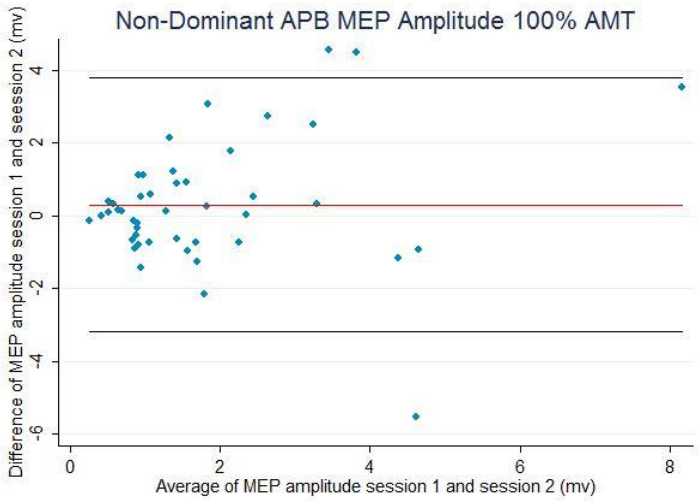


Figure 70 A. Bland-Altman plot of the average MEP amplitude of the non-dominant APB during 100% AMT, n=47

B

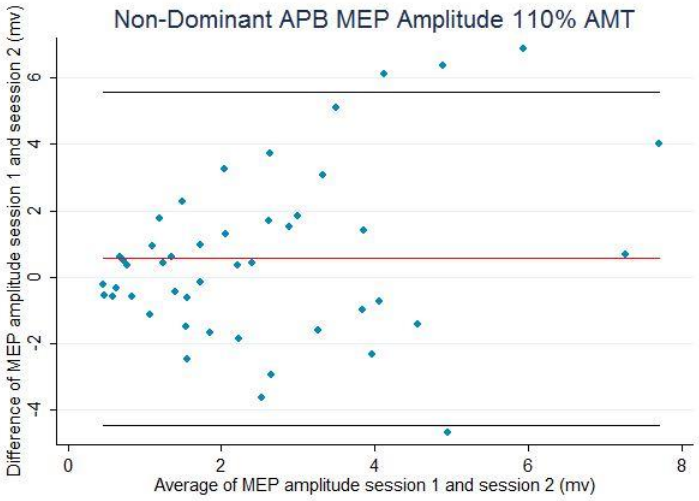


Figure 70 B. Bland-Altman plot of the average MEP amplitude of the non-dominant APB during 110% AMT, n=48

Figure 70 A & B - Bland-Altman Plots of the average MEP amplitude of the APB muscle during active conditions (20%MVC) at 100% and 110% of AMT. The x axis is the average MEP amplitude measured in mv of session 1 and session 2 plotted against the difference in average MEP amplitude (mv) between session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A and B demonstrate a potential association that as amplitude increases the difference in measurement between sessions increases. MEP= motor evoked potential, AMT=Active motor threshold, APB=abductor pollicis brevis

Figure 71 - Bland-Altman Plot of the Non-Dominant Abductor Pollics Brevis Average MEP Amplitude during Active Conditions

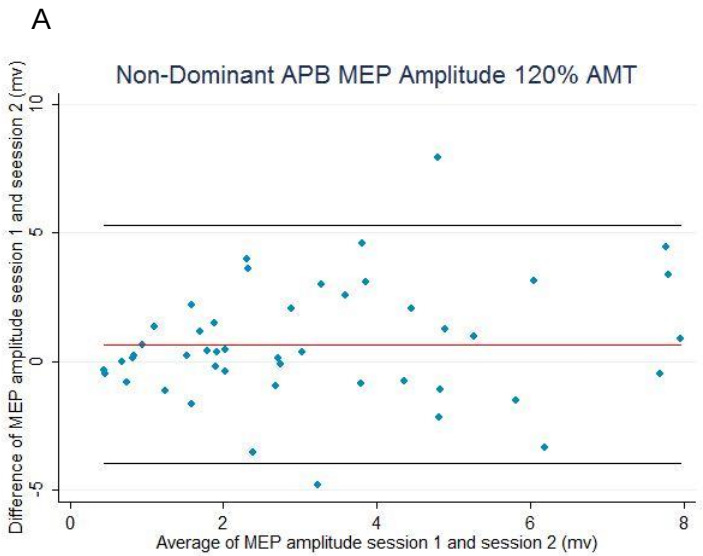


Figure 71 A. Bland-Altman plot of the average MEP amplitude of the non-dominant APB during 120% AMT n=49

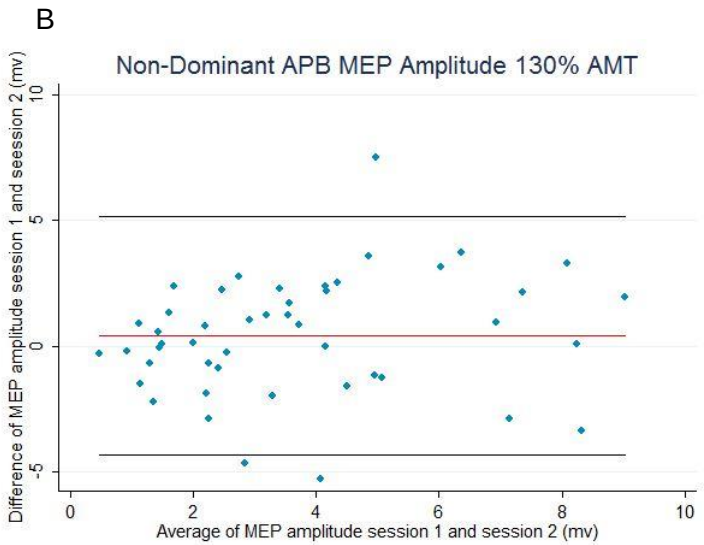


Figure 71 B. Bland-Altman plot of the average MEP amplitude of the non-dominant APB during 130% AMT, n=49

Figure 71 A & B - Bland-Altman Plots of the average MEP amplitude of the APB muscle during active conditions (20%MVC) at 120% and 130% of AMT. The x axis is the average MEP amplitude measured in mv of session 1 and session 2 plotted against the difference in average MEP amplitude (mv) between session 1 and session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A and B demonstrate random error in agreement between tests (dispersion of dots above and below the mean difference line). MEP= motor evoked potential, AMT=Active motor threshold, APB=abductor pollicis brevis

Appendix 12 - Reliability of MEP Max with Subgroups

Table 52 - MEP Max Subgroups during Active Conditions

Dominant/Non-Dominant	Participant Group	Participants	ICC (95% CI)	95 % LOA	Reliability Category
Dominant Biceps	Whole group	N=51	0.574, (0.360, 0.732)	-3.243 to 2.501	Poor
	Women	N=30	0.620, (0.340, 0.799)	-2.809 to 1.920	Poor
	Men	N=21	0.530, (0.138, 0.779)	-3.793 to 3.261	Moderate
	< 50 years of age	N=33	0.535, (0.247, 0.737)	-3.812 to 2.838	Poor
	> 50 years of age	N=18	0.629, (0.245, 0.843)	-1.935 to 1.619	Poor
	Exercisers	N=40	0.569, (0.320, 0.745)	-3.434 to 2.796	Poor
	Non-exercisers	N=11	0.547, (0.016, 0.849)	-2.350 to 1.230	Poor
Non-Dominant Biceps	Whole group	N=33	0.596, (0.385, 0.747)	-2.968 to 3.957	Poor
	Women	N=30	0.334, (-0.016, 0.614)	-3.471 to 4.316	Poor
	Men	N=21	0.797, (0.554, 0.913)	-2.215 to 3.411	Poor
	< 50 years of age	N=33	0.627, (0.369, 0.796)	-3.237 to 3.933	Poor
	> 50 years of age	N=18	0.490, (0.076, 0.768)	-2.492 to 4.018	Poor
	Exercisers	N=40	0.589, (0.348, 0.758)	-3.319 to 4.189	Poor
	Non-exercisers	N=11	0.515, (-0.019, 0.836)	-1.463 to 2.883	Poor
Dominant ECR	Whole group		0.781, (0.646, 0.869)	-2.701 to 2.507	Poor
	Women	N=30	0.762, (0.557, 0.879))	-3.619 to 3.892	Poor
	Men	N=21	0.830, (0.632, 0.927)	-2.581 to 1.900	Poor
	< 50 years of age	N=33	0.747, (0.545, 0.867)	-3.538 to 3.470	Poor
	> 50 years of age	N=18	0.830, (0.601, 0.933)	-2.903 to 2.722	Moderate
	Exercisers	N=40	0.758, (0.586, 0.864)	-3.014 to 3.151	Poor
	Non-exercisers	N=11	0.814, (0.465, 0.946)	-4.279 to 3.300	Poor

Dominant/Non-Dominant	Participant Group	Participants	ICC (95% CI)	95 % LOA	Reliability Category
Non-Dominant ECR	Whole group	N=51	0.451, (0.199, 0.645)	-2.942 to 2.967	Moderate
	Women	N=30	0.540, (0.229, 0.751	-2.849 to 2.479	Moderate
	Men	N=18	0.337, (-0.101, 0.665)	-3.015 to 3.606	Poor
	< 50 years of age	N=33	0.453, (0.139, 0.685)	-3.447 to 2.835	Poor
	> 50 years of age	N=18	0.509, (0.090, 0.780)	-1.609 to 2.803	Moderate
	Exercisers	N=39	0.359, (0.053, 0.602)	-2.904 to 3.055	Moderate
	Non-exercisers	N=11	0.667, (0.137, 0.899)	-3.171 to 2.735	Poor
Dominant APB	Whole group	N=51	0.380, (0.118, 0.592)	-4.907 to 4.522	Poor
	Women	N=30	0.386, (0.032, 0.653)	-5.145 to 4.620	Poor
	Men	N=20	0.376, (-0.071, 0.693)	-4.693 to 4.494	Poor
	< 50 years of age	N=33	0.464, (0.156, 0.692)	-4.943 to 3.917	Poor
	> 50 years of age	N=18	0.219, (95% CI: -0.276, 0.617)	-4.718 to 5.538	Poor
	Exercisers	n=40	0.322, (0.012, 0.574)	-5.064 to 4.638	Poor
	Non-exercisers	N=11	0.555, (-0.070, 0.860)	-4.413 to 4.212	Poor
Non-Dominant APB	Whole group	N=51	0.581, (0.367, 0.738)	-4.421 to 5.349	Moderate
	Women	N=30	0.618, (0.304, 0.805)	-3.323 to 5.564	Moderate
	Men	N=20	0.530, (0.142, 0.778)	-5.476 to 4.470	Poor
	< 50 years of age	N=32	0.459, (0.132, 0.695)	-5.652 to 6.000	Poor
	> 50 years of age	N=18	0.815, (0.448, 0.934)	-1.743 to 3.608	Poor
	Exercisers	N=38	0.516, (0.247, 0.712)	-4.743 to 5.743	Poor
	Non-exercisers	N=11	0.835, (0.505, 0.953)	-2.841 to 3.465	Poor

Table 53 - MEP Max Subgroups at Rest

Dominant/Non-Dominant	Participant Group	Participants	ICC (95% CI)	95 % LOA	Reliability Category
Dominant Biceps	Whole group	47	0.180 (-0.097, 0.436)	-2.554 to 3.394	Poor
	Women	27	0.077, (-0.285, 0.430)	-2.604 to 3.517	Poor
	Men	20	0.301, (-0.147, 0.649)	-2.569 to 3.293	Moderate
	< 50 years of age	32	0.098, (-0.255, 0.428)	-2.934 to 3.494	Poor
	> 50 years of age	15	0.424, (-0.032, 0.752)	-1.445 to 2.998	Poor
	Exercisers	33	0.155, (-0.160, 0.448)	-2.622 to 3.584	Poor
	Non-exercisers	14	0.290, (-0.388, 0.748)	-2.405 to 2.837	Poor
Dominant ECR	Whole group	50	0.487, (0.242, 0.673**)**	-3.243 to 2.501	Poor
	Women	29	0.605, (0.320, 0.792)	-1.987 to 2.582	Poor
	Men	21	0.373, (-0.016, 0.677)	-3.335 to 1.996	Poor
	< 50 years of age	33	0.420, (0.093, 0.664)	-3.055 to 2.695	Poor
	> 50 years of age	17	0.649, (0.251, 0.858)	-1.982 to 2.100	Poor
	Exercisers	39	0.525, (0.252, 0.720)	-2.339 to 2.431	Poor
	Non-exercisers	11	0.442, (-0.133, 0.807	-3.771 to 2.588	Poor
Dominant APB	Whole group	49	0.330, (0.053, 0.559)	-4.391 to 4.564	Poor
	Women	29	0.286, (-0.094, 0.590)	-4.895 to 5.106	Poor
	Men	20	0.327, (-0.143, 0.670)	-3.724 to 3.844	Poor
	< 50 years of age	32	0.320, (-0.035, 0.601)	-4.496 to 4.739	Poor
	> 50 years of age	17	0.362, (-0.154, 0.715)	-4.332 to 4.379	Moderate
	Exercisers	39	0.270, (-0.051, 0.539)	-4.538 to 4.240	Poor
	Non-exercisers	10	0.440, (-0.144, 0.817)	-3.472 to 5.629	Poor

Appendix 13: Bland-Altman Plots of MEP Max Amplitude

Figure 72 - Bland-Altman plots of Amplitude of MEP Max of the Biceps Muscle

A

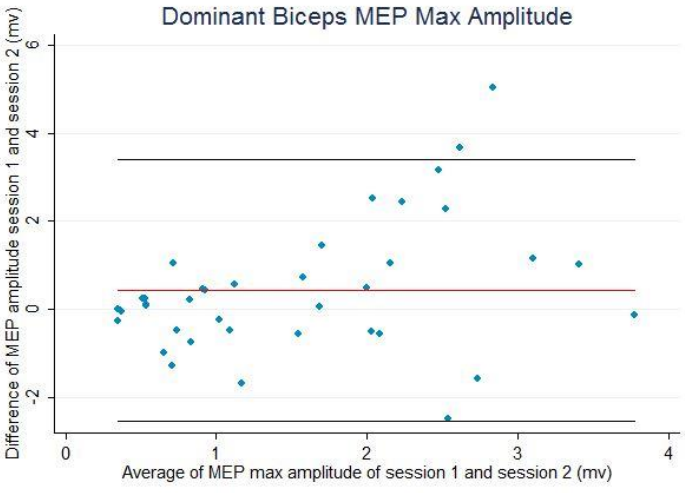


Figure 72 A. Bland-Altman plot of the MEP max of the dominant biceps during resting conditions, n=47

B

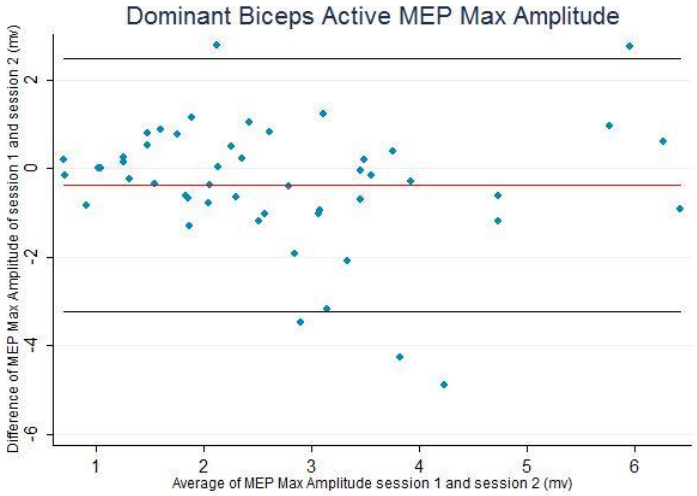


Figure 72 B. Bland-Altman plot of the MEP max of the dominant biceps during active conditions, n=51

C

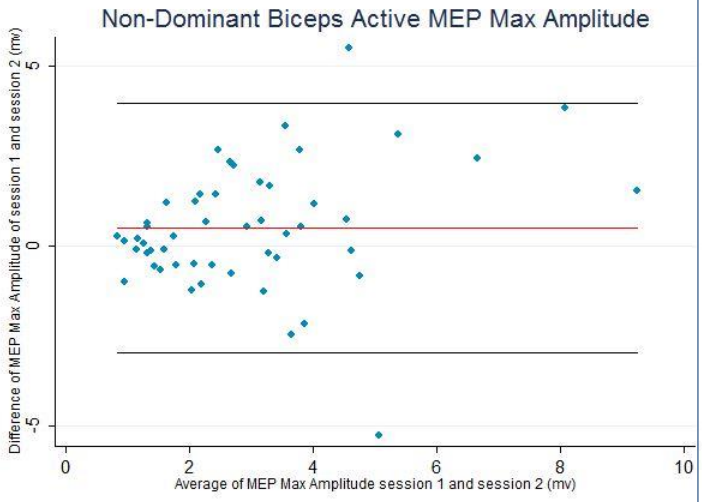


Figure 72 C. Bland-Altman plot of the MEP max of the non-dominant biceps during active conditions, n=51

Figure 72 A, B, & C - Bland-Altman Plots of the 95% LOA of the amplitude of MEP max of the biceps muscle during active (20% MVC) conditions and resting conditions. The x axis is the average amplitude of MEP max measured in mv of session 1 and session 2 plotted against the difference in amplitude of MEP max (mv) between session 1 and session 2. The red line is the mean difference in MEP max amplitude between session 1 and session 2. Plots A, B and C demonstrate demonstrate a potential association that as amplitude increases the difference in measurement between sessions increases. MEP= motor evoked potential, LOA= limits of agreement

Figure 73 - Bland-Altman Plots of Amplitude of MEP Max of the Extensor Carpi Radialis Muscle

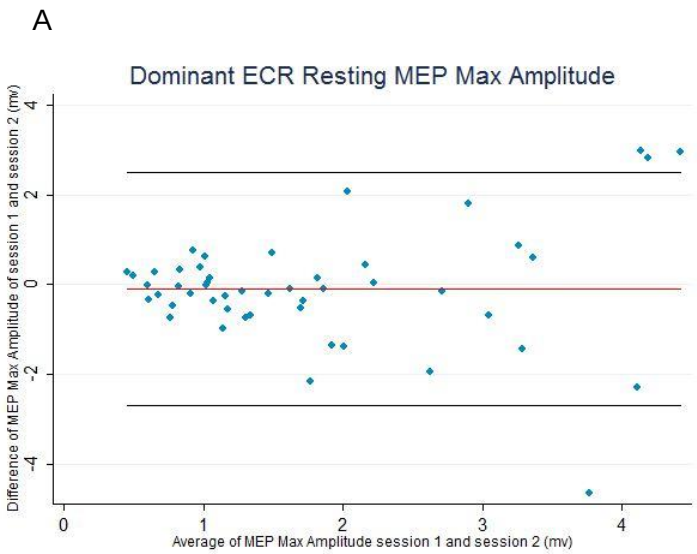


Figure 73 A. Bland-Altman plot of the MEP max of the dominant ECR during resting conditions, n=50

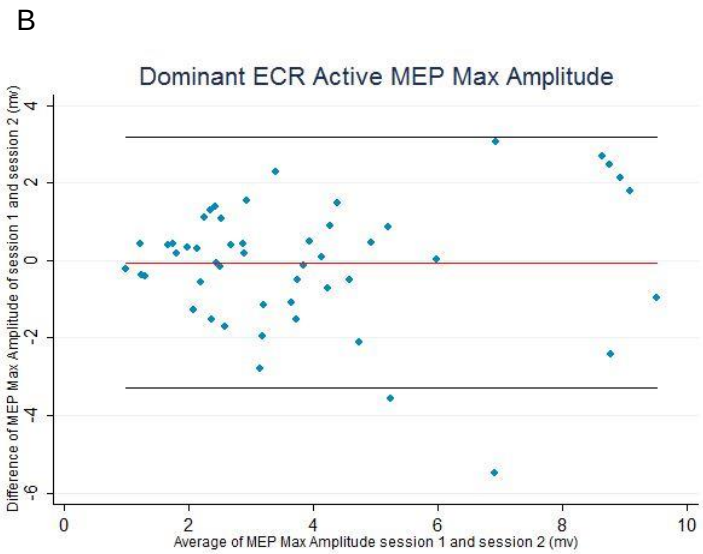


Figure 73 B. Bland-Altman plot of the MEP max of the dominant ECR during active conditions, n=51

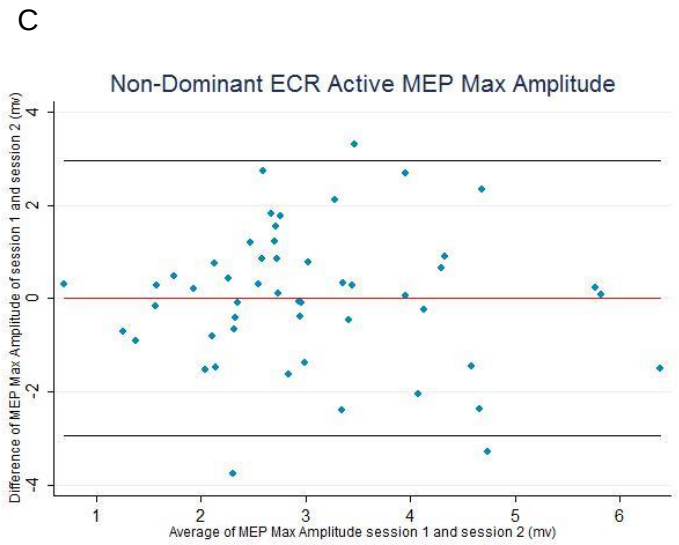


Figure 73 C. Bland-Altman plot of the MEP max of the non-dominant ECR during active conditions, n=51

Figure 73 A, B, & C - Bland-Altman Plots of MEP Max Amplitude of the ECR during active conditions (20% MVC). The x axis is the average amplitude of MEP max measured in mv of session 1 and session 2 plotted against the difference in amplitude of MEP max (mv) between session 1 and session 2. The red line is the mean difference in MEP max amplitude between session 1 minus session 2. Plots A, B and C demonstrate a potential association that as amplitude increases the difference in measurement between sessions increases. MEP= motor evoked potential, ECR= extensor carpi radialis

Figure 74 - Bland-Altman Plots of Amplitude of MEP Max of the Abductor Pollicis Brevis

A

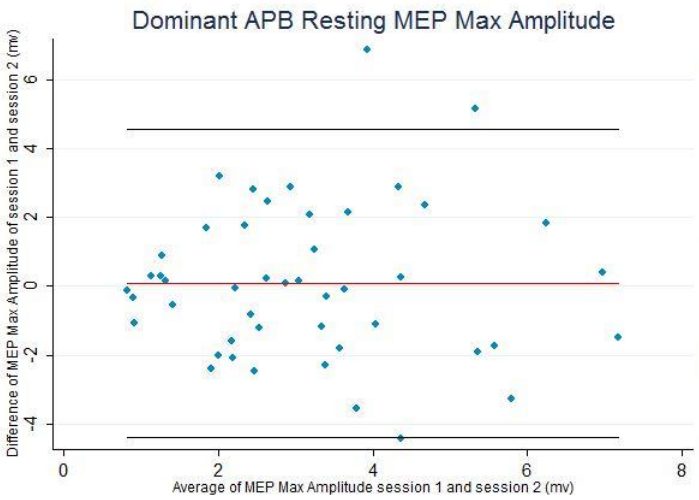


Figure 74 A. Bland-Altman plot of the MEP max of the dominant APB during resting conditions, n=49

B

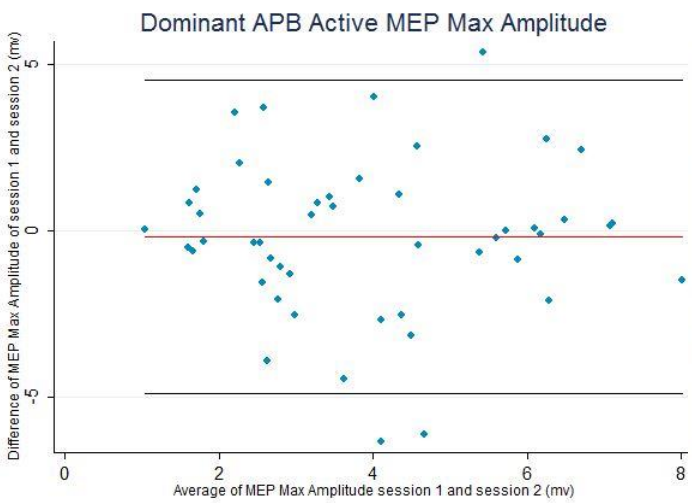


Figure 74 B. Bland-Altman plot of the MEP max of the dominant APB during active conditions, n=51

C

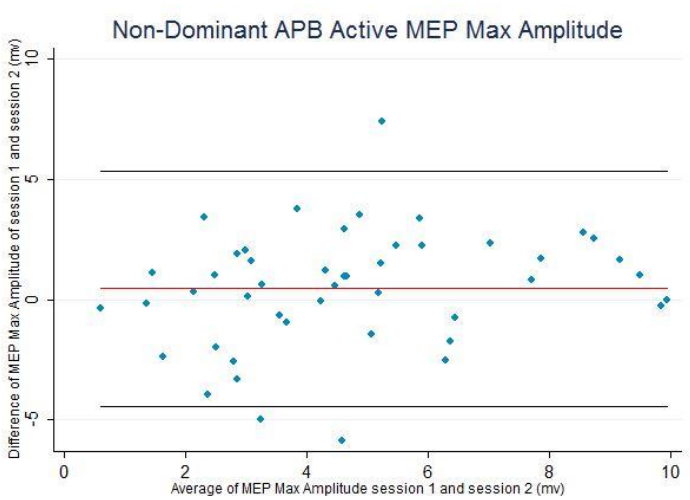


Figure 74 C. Bland-Altman plot of the MEP max of the non-dominant APB during active conditions, n=51

Figure 74 A, B, & C - Bland-Altman Plots of MEP Max Amplitude of the APB during active conditions (20% MVC). The x axis is the average amplitude of MEP max measured in mv of session 1 and session 2 plotted against the difference in amplitude of MEP max (mv) between session 1 and session 2. The red line is the mean difference in MEP max amplitude between session 1 and session 2. Plots A, B and C demonstrate random error in agreement between ratings. MEP= motor evoked potential, APB= abductor pollicis brevis

Appendix 14 - Reliability of the Silent Period Including Subgroups

Table 54- Silent Period assessed at 130% AMT

(next page)

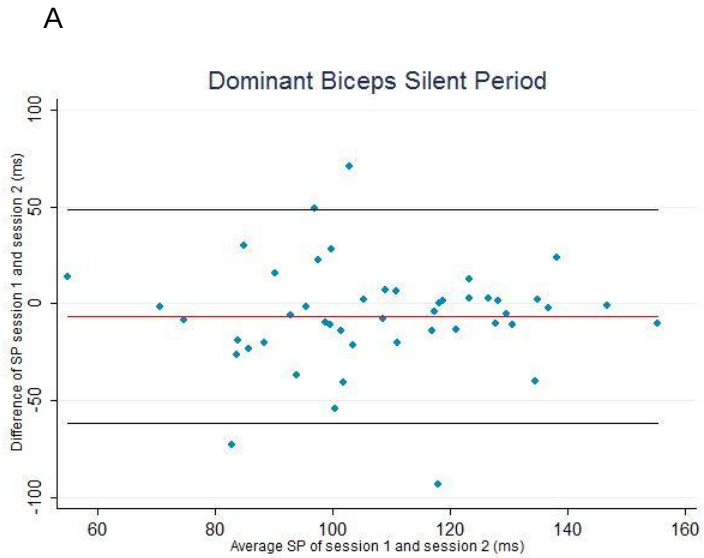
Dominant/Non-Dominant	Participant Group	Participants	ICC (95% CI)	95 % LOA	Reliability Category
Dominant Biceps	Whole group	N=51	0.614, (0.412, 0.759)	-47.343 to 36.131	Poor
	Women	N=30	0.480, (0.159, 0.712)	-47.795 to 40.124	Poor
	Men	N=21	0.789, (0.556, 0.908)	-47.424 to 32.510	Moderate
	< 50 years of age	N=33	0.558, (0.206, 0.769)	-51.416 to 35.687	Poor
	> 50 years of age	N=18	0.710, (0.380, 0.881)	-34.331 to 35.543	Poor
	Exercisers	N=40	0.556, (0.301, 0.737)	-39.661 to 34.986	Poor
	Non-exercisers	N=11	0.788, (0.250, 0.943)	-65.441 to 34.025	Poor
Non-Dominant Biceps	Whole group	N=33	0.537, (0.311, 0.706)	53.809 to 46.4212	Poor
	Women	N=30	0.503, (0.184, 0.727)	-50.122 to 47.764	Poor
	Men	N=21	0.588, (0.214, 0.811)	-58.246 to 45.602	Poor
	< 50 years of age	N=33	0.474, (0.166, 0.699)	-54.343 to 46.409	Poor
	> 50 years of age	N=18	0.657, (0.278, 0.857)	-54.540 to 48.843	Poor
	Exercisers	N=40	0.570, (0.320, 0.746)	-46.627 to 44.049	Poor
	Non-exercisers	N=11	0.372, (-0.310, 0.786)	-73.941 to 51.689	Poor
Dominant ECR	Whole group		0.656, (0.465, 0.788)	-47.725 to 46.062	Poor
	Women	N=30	0.600, (0.313, 0.787)	-43.998 to 44.448	Poor
	Men	N=21	0.709, (0.408, 0.871)	-53.131 to 48.853	Poor
	< 50 years of age	N=33	0.501, (0.190, 0.719)	-46.262 to 46.254	Poor
	> 50 years of age	N=18	0.834, (0.611, 0.934)	-54.374 to 47.295	Moderate
	Exercisers	N=40	0.672, (0.459, 0.812)	-45.344 to 47.699	Poor
	Non-exercisers	N=11	0.605, (0.091, 0.873)	-55.916 to 39.384	Poor
Non-Dominant ECR	Whole group	N=51	0.750, (0.598, 0.850)	-52.759 to 49.966	Moderate
	Women	N=30	0.767, (0.564, 0.882)	-64.023 to 41.146	Moderate
	Men	N=20	0.704, (0.389, 0.872)	-60.180 to 47.163	Poor
	< 50 years of age	N=33	0.718, (0.498, 0.851)	-55.646 to 52.309	Poor
	> 50 years of age	N=18	0.859, (0.668, 0.944)	-45.275 to 44.113	Moderate
	Exercisers	N=39	0.788, (0.631, 0.883)	-46.508 to 51.299	Moderate
	Non-exercisers	N=11	0.477, (-0.097, 0.823)	-66.713 to 41.167	Poor
Dominant APB	Whole group	N=51	0.647, (0.423, 0.791)	-61.976 to 39.810	Poor
	Women	N=30	0.635, (0.288, 0.821)	-64.023 to 41.146	Poor
	Men	N=20	0.692, (0.375, 0.865)	-60.789 to 39.474	Poor
	< 50 years of age	N=33	0.601, (0.326, 0.781)	-59.740 to 39.400	Poor
	> 50 years of age	N=17	0.714, (0.355, 0.888)	-70.659 to 43.013	Poor
	Exercisers	n=40	0.654, (0.417, 0.805)	-62.615 to 42.219	Poor
	Non-exercisers	N=11	0.623, (0.090, 0.888)	-61.738 to 34.259	Poor
Non-Dominant APB	Whole group	N=51	0.769, (0.589, 0.870)	-69.659 to 66.889	Moderate
	Women	N=30	0.750, (0.534, 0.874)	-60.852 to 60.264	Moderate

Men	N=20	0.443, (0.017, 0.734)	-80.255 to 74.992	Poor
< 50 years of age	N=33	0.670, (0.415, 0.826)	-72.324 to 69.296	Poor
> 50 years of age	N=18	0.527, (0.085, 0.793)	-63.935 to 61.962	Poor
Exercisers	N=38	0.613, (0.365, 0.779)	-61.910 to 60.818	Poor
Non-exercisers	N=11	0.691, (0.177, 0.907)	-93.669 to 85.712	Poor

Table 54- Test-retest reliability of the silent period assessed 130% AMT, with 20% MVC background contraction (assessed individually for each participant at each session) for participants based on gender, age, and participation in exercise. The test-retest reliability was determined using the ICC model [2,1] and associated 95% CI, and Bland-Altman's 95% LOA. The ICC is interpreted such that ICC > 0.7 is acceptable reliability, based on the lower end of the confidence interval.

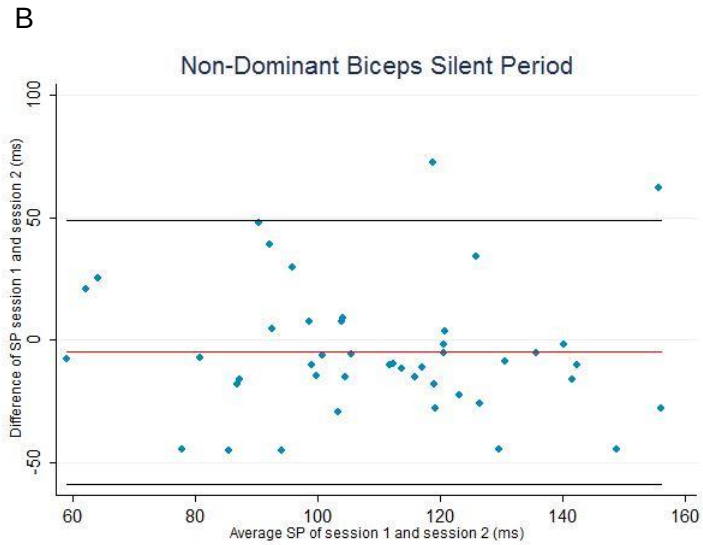
Appendix 15: Bland-Altman Plots of the Silent Period

Figure 75 - Bland-Altman Plots of the Silent Period of the Biceps Muscle during 130% AMT



Appendix 15: Bland-Altman Plots of the Silent Period

Figure 75 A. Bland-Altman plot of the silent period



Appendix 15: Bland-Altman Plots of the Silent Period

Figure 75 B. Bland-Altman plot of the silent period of the non-dominant biceps muscle assessed at

Figure 75 A & B - Bland-Altman Plots of the silent period of the dominant (A) and non-dominant (B) biceps muscle assessed at 130% AMT. The x axis is the average silent period measured in ms of session 1 and session 2 plotted against the difference in silent period in ms between session 1 minus session 2. The red line is the mean difference of the silent period between session 1 and session 2. Plots A and B demonstrate random error in agreement between tests. Note difference in scale between plot A and plot B. MEP= motor evoked potential, AMT=Active motor threshold, SP=silent period, APB= abductor pollicis brevis

Figure 76 - Bland-Altman Plot of the Silent Period of the Extensor Carpi Radialis

A

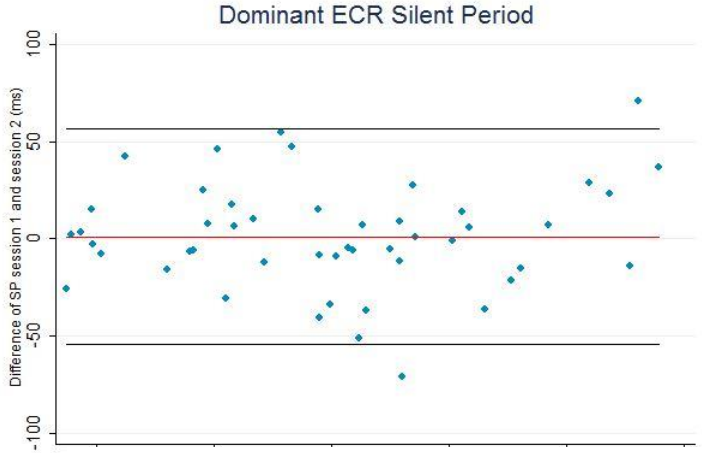


Figure 76 A. Bland-Altman plot of the silent period of the dominant ECR assessed during 130% AMT, n=51

B

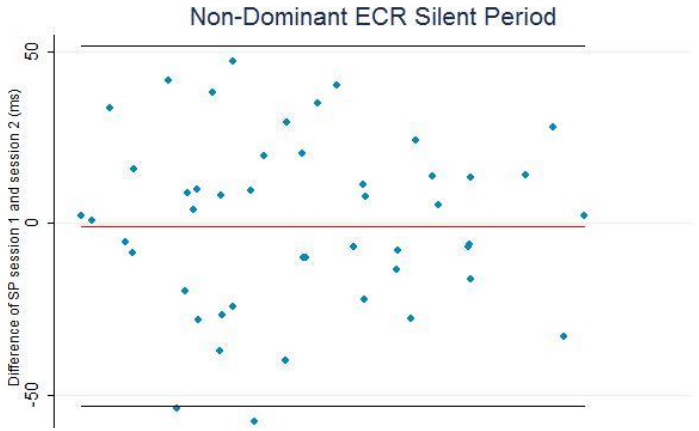


Figure 76 B. Bland-Altman plot of the silent period of the non-dominant ECR assessed during 130% AMT, n=51

Figure 76 A & B - Bland-Altman Plots of the silent period of the dominant (A) and non-dominant (B) ECR muscle assessed at 130% AMT. The x axis is the average silent period measured in ms of session 1 and session 2 plotted against the difference in silent period in ms between session 1 minus session 2. The red line is the mean difference of the silent period between session 1 and session 2. Plots A and B demonstrate random error in agreement between tests. MEP= motor evoked potential, AMT=Active motor threshold, SP=silent period, ECR=extensor carpi radialis

Figure 77 - Bland-Altman Plots of the Silent Period of the Abductor Pollicis Brevis Muscle

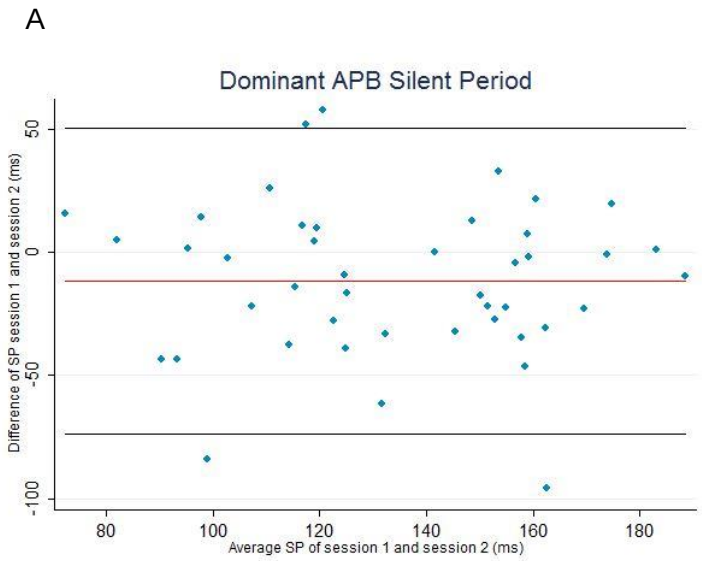


Figure 77 A. Bland-Altman plot of the silent period of the dominant APB assessed during 130% AMT, n=51

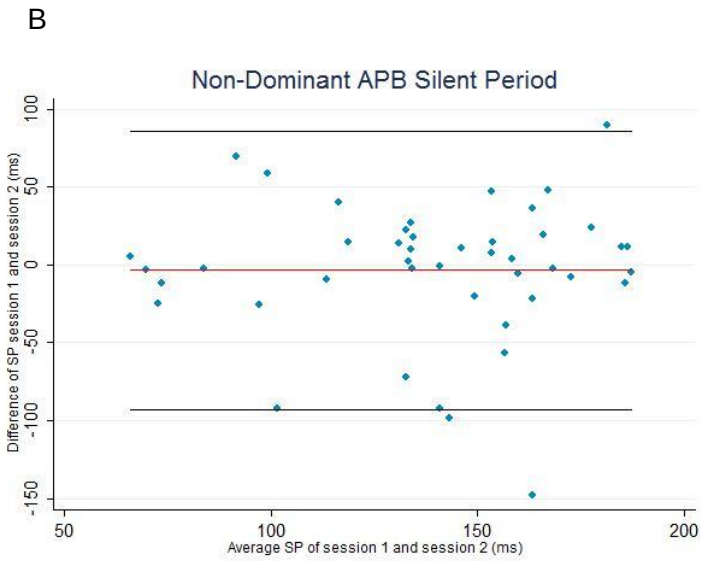


Figure 77 B. Bland-Altman plot of the silent period of the non-dominant APB assessed during 130% AMT, n=51

Figure 77 A & B - Bland-Altman Plots of the silent period of the dominant (A) and non-dominant (B) APB muscle assessed at 130% AMT. The x axis is the average silent period measured in ms of session 1 and session 2 plotted against the difference in silent period in ms between session 1 minus session 2. The red line is the mean difference of the silent period between session 1 and session 2. Plots A and B demonstrate random error in agreement between tests. Note difference in scale between plot A and plot B. MEP= motor evoked potential, AMT=Active motor threshold, SP=silent period, APB= abductor pollicis brevis

Appendix 16: Reliability of MEP Latency of Subgroups

Table 55 - MEP Latency Assessed at 120% AMT

Dominant/Non-Dominant	Participant Group	Participants	ICC (95% CI)	95 % LOA	Reliability Category
Dominant Biceps	Whole group	N=51	0.589, (0.375, 0.743)	-2.708 to 2.603	Poor
	Women	N=30	0.773, (0.577, 0.885)	-1.608 to 1.835	Poor
	Men	N=21	0.406, (0, 0.708)	-3.886 to 3.307	Moderate
	< 50 years of age	N=34	0.506, (0.200, 0.722)	-2.862 to 2.627	Poor
	> 50 years of age	N=17	0.651, (0.270, 0.855)	-2.478 to 2.611	Poor
	Exercisers	N=40	0.483, (0.203, 0.690)	-2.793 to 2.628	Poor
	Non-exercisers	N=11	0.797, (0.396, 0.941)	-2.502 to 2.616	Poor
Non-Dominant Biceps	Whole group	N=51	0.614, (0.410, 0.760)	-2.338 to 2.123	Poor
	Women	N=30	0.567, (0.261, 0.768)	-2.459 to 2.351	Poor
	Men	N=21	0.624, (0.277, 0.828)	-2.186 to 1.818	Poor
	< 50 years of age	N=34	0.497, (0.187, 0.716)	-2.504 to 2.310	Poor
	> 50 years of age	N=17	0.755, (0.456, 0.901)	-2.055 to 1.803	Poor
	Exercisers	N=40	0.540, (0.281, 0.726)	-2.424 to 2.053	Poor
	Non-exercisers	N=11	0.775, (0.360, 0.934)	-2.030 to 2.383	Poor
Dominant ECR	Whole group	N=50	0.653, (0.464, 0.786)	-2.398 to 3.030	Poor
	Women	N=30	0.728, (0.506, 0.860)	-2.191 to 2.835	Poor
	Men	N=20	0.461, (0.051, 0.739)	-2.751 to 3.365	Poor
	< 50 years of age	N=33	0.546, (0.262, 0.745)	-2.263 to 3.027	Poor
	> 50 years of age	N=17	0.592, (0.184, 0.826)	-2.696 to 3.092	Moderate
	Exercisers	N=39	0.637, (0.412, 0.790)	-2.480 to 2.934	Poor
	Non-exercisers	N=11	0.716, (0.271, 0.913)	-2.140 to 3.403	Poor
Non-Dominant ECR	Whole group	N=51	0.560, (0.337, 0.723)	-2.242 to 3.126	Moderate
	Women	N=30	0.626, (0.353, 0.802)	-2.209 to 3.113	Moderate
	Men	N=21	0.352, (0, 0.669)	-2.358 to 3.214	Poor
	< 50 years of age	N=34	0.558, (0.270, 0.755)	-2.188 to 2.439	Poor
	> 50 years of age	N=17	0.383, (0, 0.705)	-1.950 to 4.026	Moderate
	Exercisers	N=40	0.464, (0.190, 0.673)	-2.350 to 3.067	Moderate
	Non-exercisers	N=11	0.716, (0.253, 0.914)	-1.851 to 3.386	Poor
Dominant APB	Whole group	N=49	0.563 (0.345, 0.725)	-4.754 to 4.068	Poor
	Women	N=28	0.327, (0, 0.604)	-5.679 to 3.893	Poor
	Men	N=21	0.794, (0.563, 0.910)	-3.113 to 3.857	Poor
	< 50 years of age	N=33	0.596, (0.324, 0.778)	-4.170 to 3.639	Poor
	> 50 years of age	N=16	0.432, (0, 0.742)	-5.852 to 4.874	Poor
	Exercisers	N=40	0.529, (0.267, 0.719)	-4.820 to 4.006	Poor
	Non-exercisers	N=9	0.650, (0.089, 0.893)	-4.712 to 4.547	Poor
Non-Dominant APB	Whole group	N=49	0.697 (0.523, 0.815)	3.388 to 3.512	Moderate
	Women	N=28	0.751, (0.543, 0.873)	-2.933 to 3.543	Moderate
	Men	N=21	0.534, (0.142, 0.781)	-4.009 to 3.417	Poor

	< 50 years of age	N=32	0.541, (0.244, 0.745)	-3.044 to 3.193	Poor
	> 50 years of age	N=17	0.771, (0.481, 0.908)	-3.982 to 4.067	Poor
	Exercisers	N=38	0.574, (0.321, 0.750)	-3.479 to 3.219	Poor
	Non-exercisers	N=11	0.844, (0.537, 0.955)	-2.714 to 4.465	Poor

Table 56 - MEP Latency Assessed at 120% RMT

Dominant/Non-Dominant	Participant Group	Participants	ICC (95% CI)	95 % LOA	Reliability Category
Dominant Biceps	Whole group	N=38	0.436 (0.152, 0.653)	-5.215 to5.498	Poor
	Women	N=21	0.447, (0.072, 0.709)	-5.574 to 5.171	Poor
	Men	N=17	0.454, (0, 0.766)	-4.174 to 6.257	Moderate
	< 50 years of age	N=31	0.422, (0.080, 0.674)	-5.485 to 5.908	Poor
	> 50 years of age	N=7	0.365, (0, 0.784)	-4.554 to 4.398	Poor
	Exercisers	N=28	0.528, (0.226, 0.736)	-4.118 to 4.122	Poor
	Non-exercisers	N=10	0.297, (0.495, 0.790)	-8.506 to 9.857	Poor
Dominant ECR	Whole group	N=49	0.492, (0.251, 0.675)	-3.497 to4.041	Poor
	Women	N=29	0.550, (0, 0.759)	-3.395 to 4.294	Poor
	Men	N=210	0.326, (0, 0.663)	-3.685 to 3.685	Poor
	< 50 years of age	N=33	0.312, (0, 0.588)	-3.806 to 4.571	Poor
	> 50 years of age	N=16	0.685, (0.311, 0.874)	-2.855 to 2.995	Poor
	Exercisers	N=38	0.653, (0.426, 0.802)	-2.640 to 2.606	Poor
	Non-exercisers	N=11	0.317, (0, 0.746)	-4.888 to 7.625	Poor
Dominant APB	Whole group	N=45	0.631 (0.426, 0.774)	-4.228 to 4.278	Poor
	Women	N=27	0.715, (0.477, 0.855)	-3.014 to 3.364	Poor
	Men	N=18	0.554, (0.150, 0.797)	-5.755 to 5.364	Poor
	< 50 years of age	N=30	0.522, (0.226, 0.732)	-5.032 to 3.665	Poor
	> 50 years of age	N=15	0.745, (0.175, 0.917)	-1.234 to 3.900	Moderate
	Exercisers	N=33	0.699, (0.497, 0.829)	-2.931 to 3.569	Poor
	Non-exercisers	N=7	0.567, (0, 0.870)	-8.186 to 5.716	Poor

Appendix 17: Bland-Altman plots of MEP Latency

Figure 78 - Bland-Altman Plots of the MEP Latency of the Biceps Muscle during Active Conditions

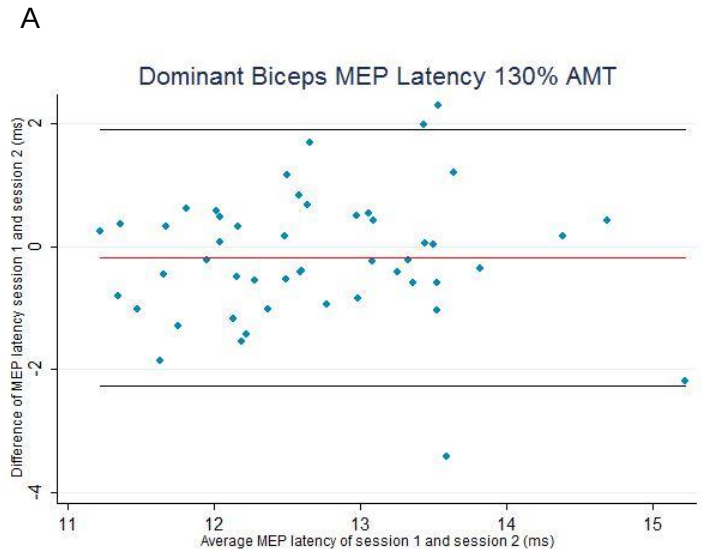


Figure 78 A. Bland-Altman plot of MEP latency of the dominant biceps during 130% AMT, n=51

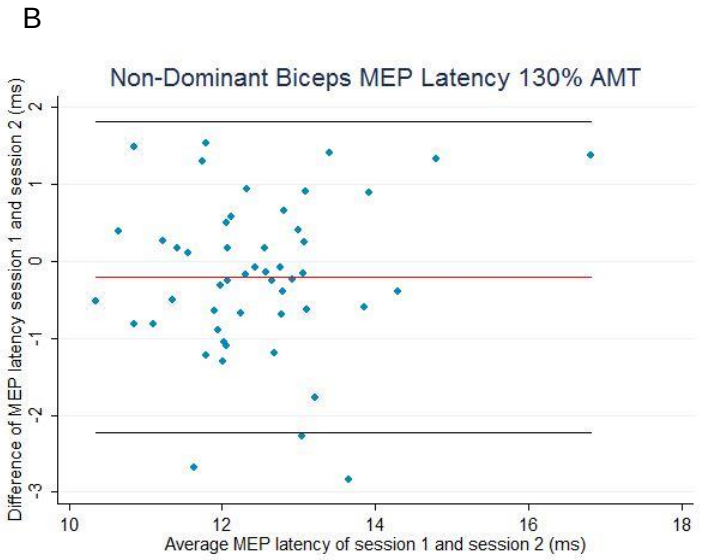


Figure 78 B. Bland-Altman plot of MEP latency of the non-dominant biceps during 130% AMT, n=51

Figure 78 A & B - Bland-Altman Plots of MEP latency of the dominant (A) and non-dominant (B) biceps muscle assessed at 130% AMT. The x axis is the average latency measured in ms of session 1 and session 2 plotted against the difference in latency in ms between session 1 minus session 2. The red line is the mean difference of the latency between session 1 and session 2. Plots A and B demonstrate random error in agreement between sessions Note the different scales of plot A and plot B. MEP= motor evoked potential. AMT=Active motor threshold

Figure 79 - Bland-Altman Plots of MEP Latency of the Extensor Carpi Radialis

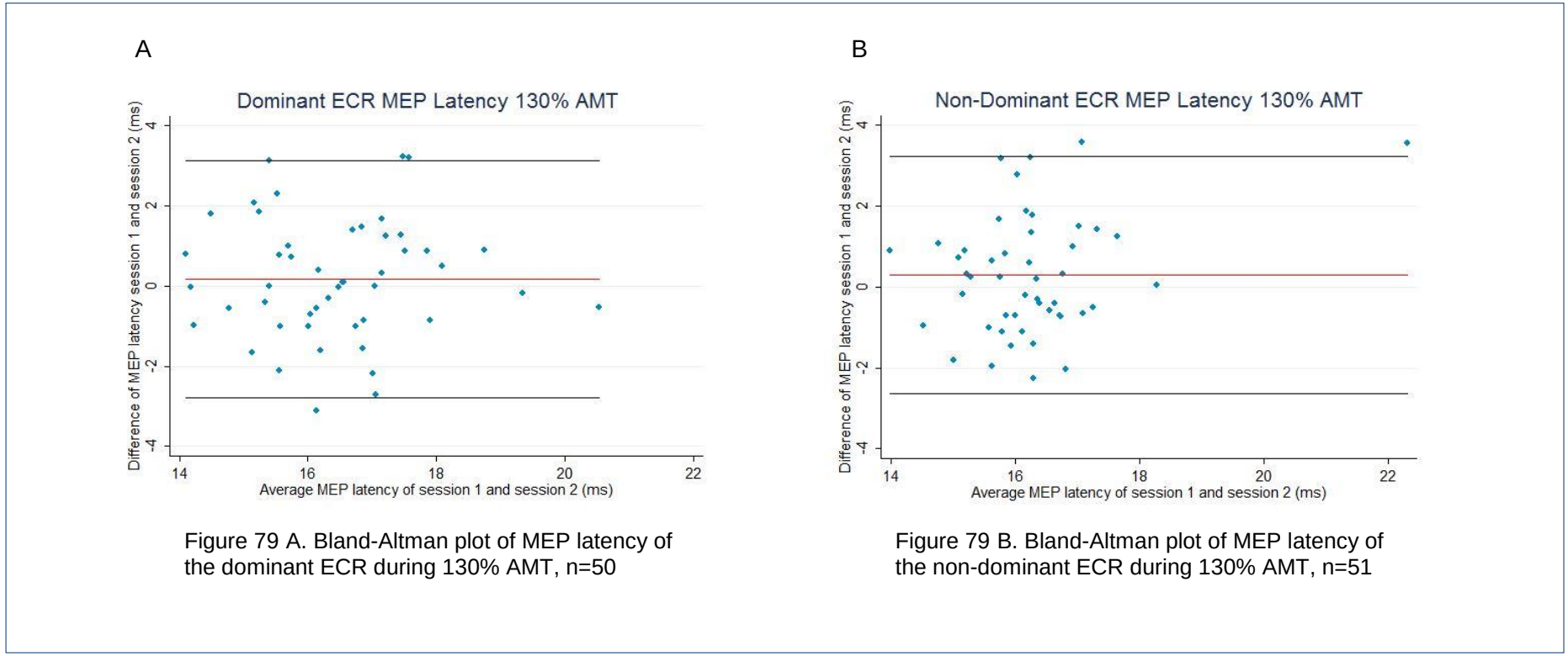


Figure 79 A. Bland-Altman plot of MEP latency of the dominant ECR during 130% AMT, n=50

Figure 79 B. Bland-Altman plot of MEP latency of the non-dominant ECR during 130% AMT, n=51

Figure 79 A & B - Bland-Altman Plots of MEP latency of the dominant (A) and non-dominant (B) ECR muscle assessed at 130% AMT. The x axis is the average latency measured in ms of session 1 and session 2 plotted against the difference in latency in ms between session 1 minus session 2. The red line is the mean difference of the latency between session 1 and session 2. Plots A and B demonstrate random error in agreement between tests. MEP= motor evoked potential. AMT=Active motor threshold, ECR=extensor carpi radialis, ms=milliseconds

Figure 80 - Bland-Altman Plots of MEP Latency of the Abductor Pollicis Brevis

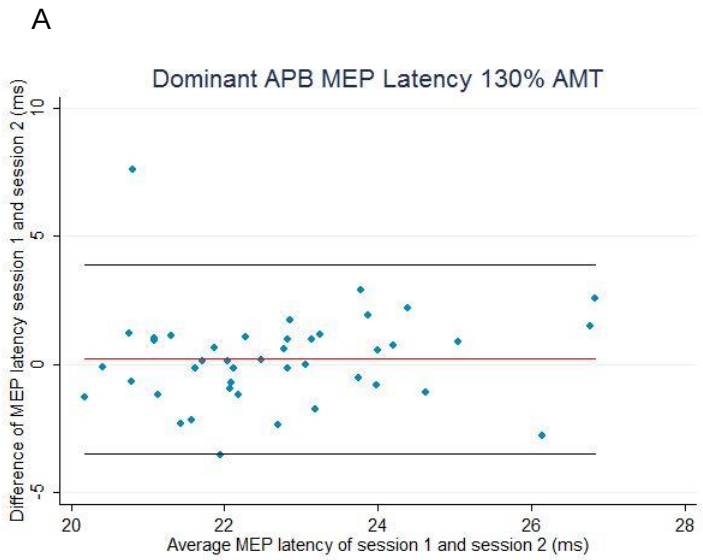


Figure 80 A. Bland-Altman plot of MEP latency of the dominant APB during 130% AMT, n=49

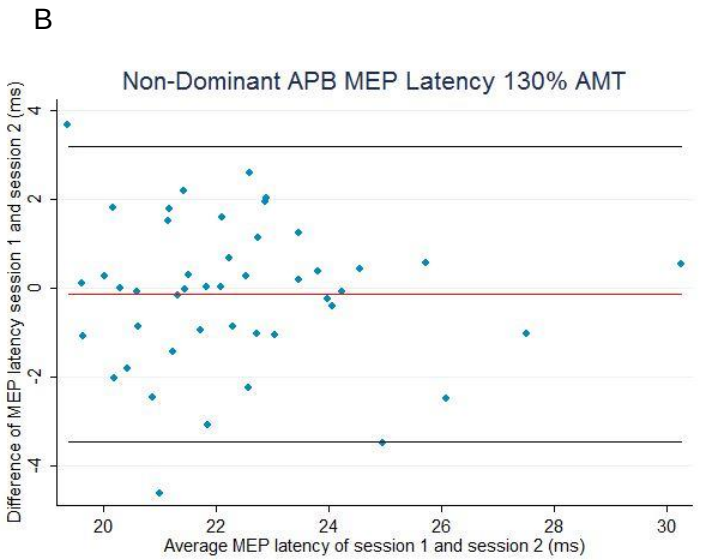


Figure 80 B. Bland-Altman plot of MEP latency of the non-dominant APB during 130% AMT, n=49

Figure 80 A & B - Bland-Altman Plots of MEP latency of the dominant (A) and non-dominant (B) APB muscle assessed at 130% AMT. The x axis is the average latency measured in ms of session 1 and session 2 plotted against the difference in latency in ms between session 1 minus session 2. The red line is the mean difference of the latency between session 1 and session 2. Plots A and B demonstrate random error in agreement between sessions. MEP= motor evoked potential. AMT=Active motor threshold, APB=abductor pollicis brevis, ms=milliseconds

Figure 81 - Bland-Altman Plots of MEP Latency of the Biceps Muscle Assessed at 120% MEP Latency

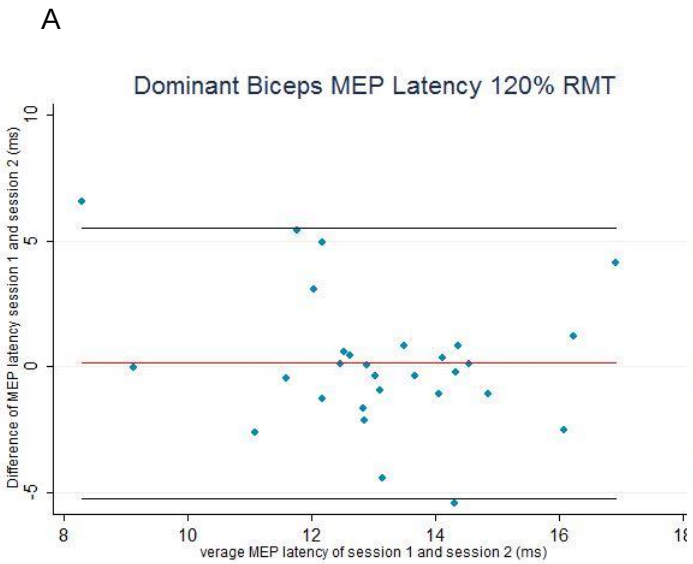


Figure 81 A. Bland-Altman plot of the MEP latency of the dominant biceps during 120% RMT, n=38

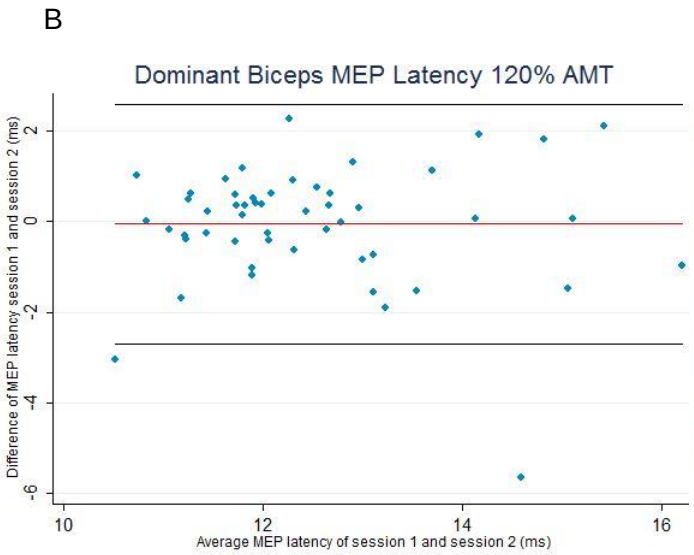


Figure 81 B. Bland-Altman plot of the MEP latency of the dominant biceps during 120% AMT. n=51

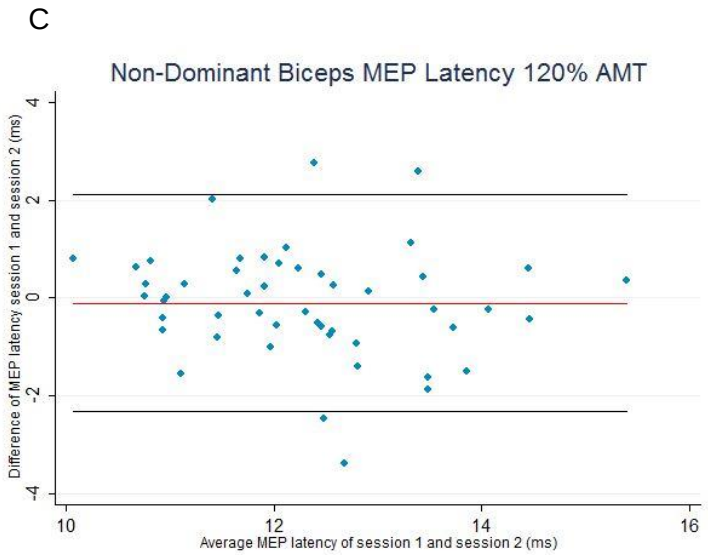


Figure 81 C. Bland-Altman plot of the MEP latency of the non-dominant biceps during 120% AMT, n=51

Figure 81 A, B, & C - Bland-Altman Plots of MEP latency of the dominant (A, B) and non-dominant (C) biceps muscle assessed at 120% of RMT and AMT. The x axis is the average latency measured in ms of session 1 and session 2 plotted against the difference in latency in ms between session 1 minus session 2. The red line is the mean difference of the latency between session 1 and session 2. Plots A, B and C demonstrate random error in agreement between sessions. Note the different scales of plot A, B, and C. MEP= motor evoked potential. AMT=Active motor threshold MEP=motor evoked potential, ms=milliseconds

Figure 82 - Bland-Altman Plots of MEP Latency of the Extensor Carpi Radialis

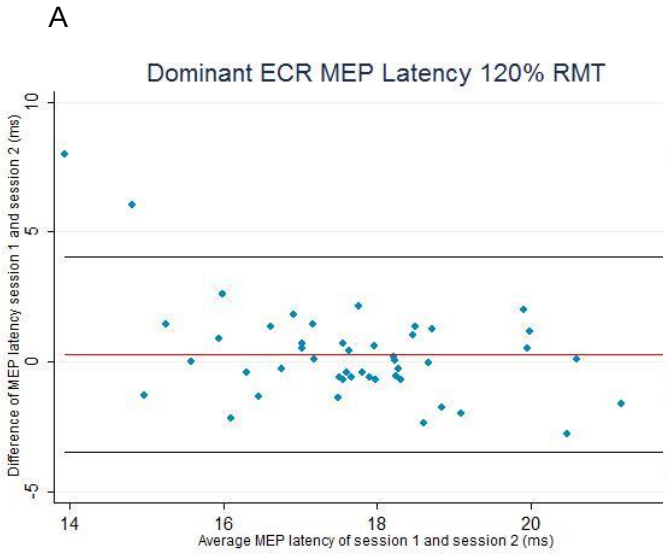


Figure 82 A. Bland-Altman plot of the MEP latency of the dominant ECR during 120% RMT, n=49

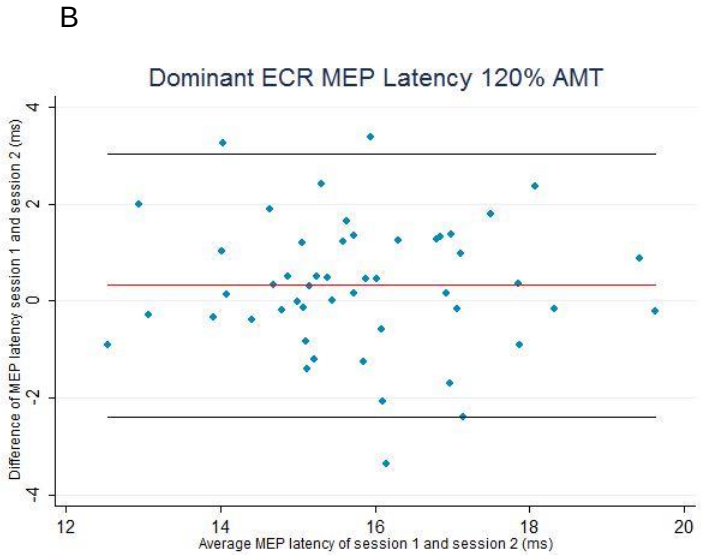


Figure 82 B. Bland-Altman plot of the MEP latency of the dominant ECR during 120% AMT, n=50

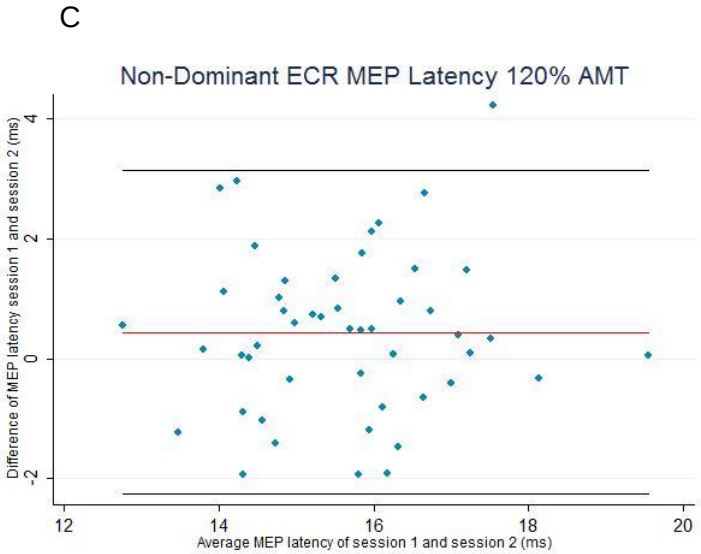


Figure 82 C. Bland-Altman plot of the MEP latency of the non-dominant ECR during 120% AMT, n=51

Figure 82 A, B, & C - Bland-Altman Plots of MEP latency of the dominant (A) and non-dominant (B) ECR muscle assessed at 120% of RMT and AMT. The x axis is the average latency measured in ms of session 1 and session 2 plotted against the difference in latency in ms between session 1 minus session 2. The red line is the mean difference of the latency between session 1 and session 2. Plots A, B, and C demonstrate random error in agreement between sessions Note the different scales of plot A compared to plot B and C. MEP= motor evoked potential. AMT=Active motor threshold, ECR=extensor radialis, ms=milliseconds

Figure 83 - Bland-Altman Plots of MEP Latency of the Abductor Pollicis Brevis

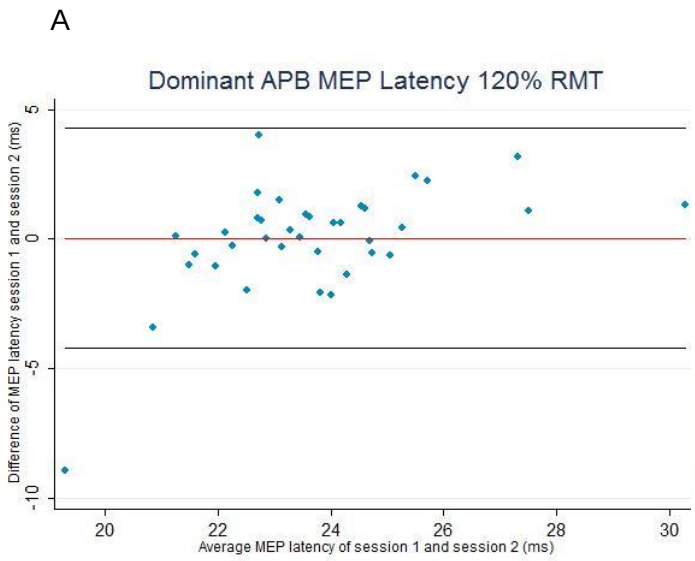


Figure 83 A. Bland-Altman plot of the MEP latency of the dominant APB during 120% RMT, n=45

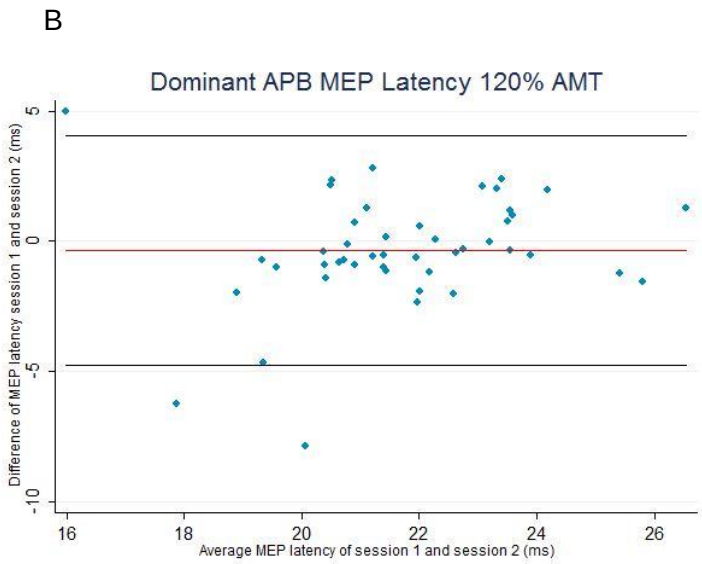


Figure 83 B. Bland-Altman plot of the MEP latency of the dominant APB during 120% AMT, n=49

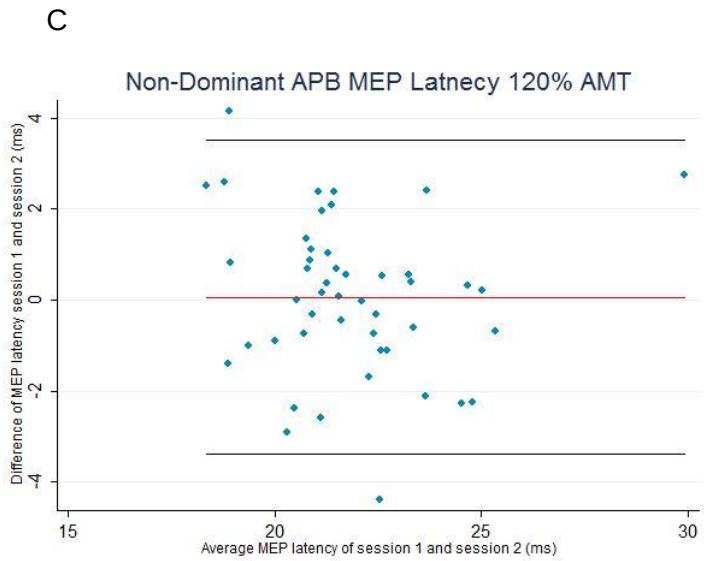


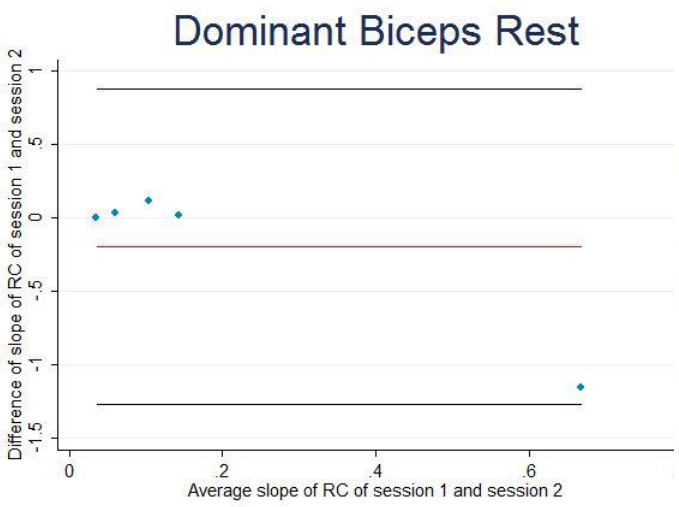
Figure 83 C. Bland-Altman plot of the MEP latency of the non-dominant APB during 120% AMT, n=49

Figure 83 A, B, & C - Bland-Altman Plots of MEP latency of the dominant (A) and non-dominant (B) APB muscle assessed at 120% of RMT and AMT. The x axis is the average latency measured in ms of session 1 and session 2 plotted against the difference in latency in ms between session 1 minus session 2. The red line is the mean difference of the latency between session 1 and session 2. Plots A, B, C demonstrate random error in agreement between sessions. Note the different scales of plot A, B and C. MEP= motor evoked potential. AMT=Active motor threshold, APB=abductor pollicis brevis

Appendix 18: Bland-Altman Plots of the slope of the recruitment curve

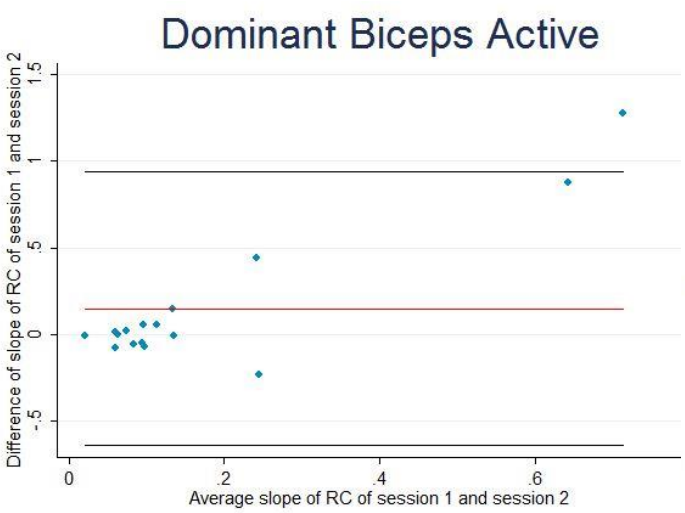
Figure 84 - Bland-Altman Plots of the Slope of the Recruitment Curve of the Biceps Muscle

A



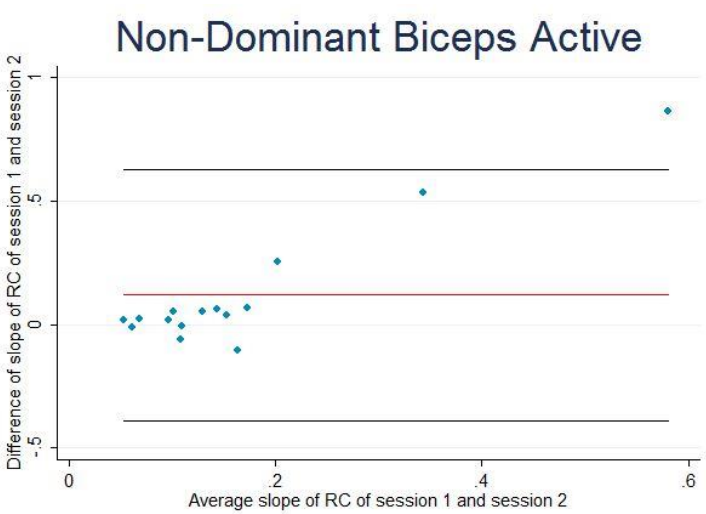
Appendix 18: Bland-Altman Plots of the slope of the recruitment curve

B



Appendix 18: Bland-Altman Plots of the slope of the recruitment curve

C



Appendix 18: Bland-Altman Plots of the slope of the recruitment curve

Figure 84 A, B, & C - Bland-Altman plot of the slope of the RC for the dominant and non-dominant biceps muscle. The active conditions are during background contraction that is 20% of participants' individual MVC which was assessed at session 1 minus session 2. The average slope of session 1 and session 2 is plotted against the difference in the slope of session 1 minus session 2. The red line is the mean difference in the slope of the RC of session 1 and session 2. Plot A exhibits systematic bias that the slope was less steep in the second session. Plots B, and C demonstrate a trend towards the slope being greater in the second session and a potential linear association. Note the different scale of plots A, B and C. RC=recruitment curve.

Figure 85 - Bland-Altman Plots of the Slope of the Recruitment Curve of the Extensor Carpi Radialis

A

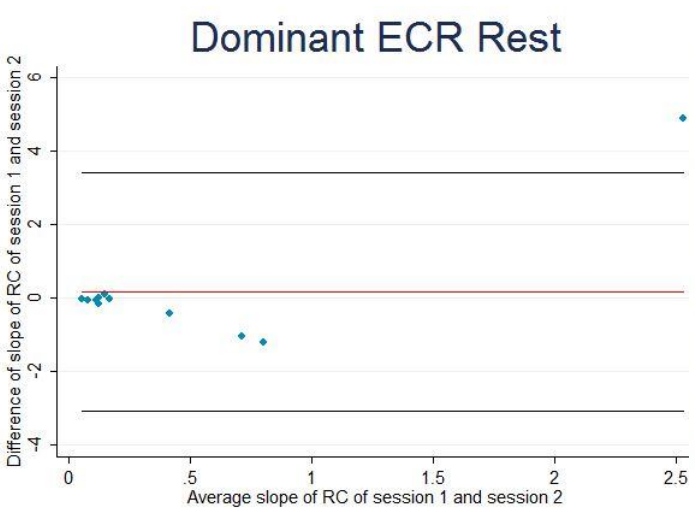


Figure 85 A. Bland-Altman plot of the slope of the RC of the dominant ECR at rest, n=11

B

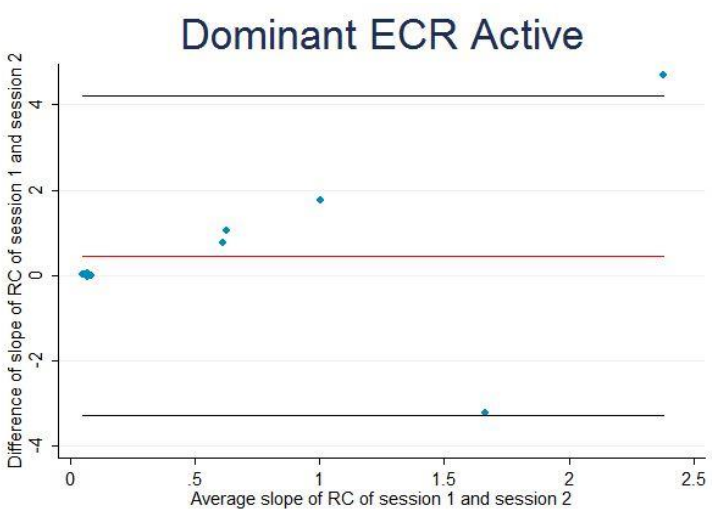


Figure 85 B. Bland-Altman plot of the slope of the RC of the dominant ECR during active conditions, n=11

C

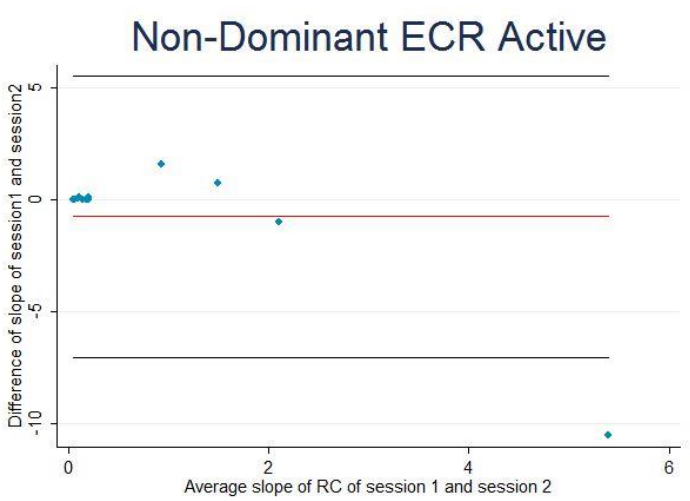


Figure 85 C. Bland-Altman plot of the slope of the RC of the non-dominant ECR during active conditions, n=12

Figure 85 A, B, & C - Bland-Altman plots of the slope of the RC of the ECR muscle assessed at rest (A) and during active conditions (B,C) which is 20% MVC calculated individually for each participant at each session. The x axis is the average slope of session 1 and session 2 plotted against the difference in the slope of session 1 minus session 2. The red line is the mean difference in slope of session 1 and session 2. Plot A exhibits systematic error such that the slope of the RC was greater the second session compared to the first. Plot B exhibits a potential association between slope and agreement. Plot C demonstrates a trend toward systematic error such that the second session demonstrated lesser slope (dot above the mean difference) The slope tended to be lower the second session during the resting conditions, and higher in the second session during the active conditions. Note the different scales of plot A, B, and C. RC=recruitment curve, ECR=extensor carpi radialis. RMT=resting motor threshold, AMT=active motor threshold

Figure 86 - Bland-Altman Plots of the Slope of the Recruitment Curve of the Abductor Pollicis Brevis

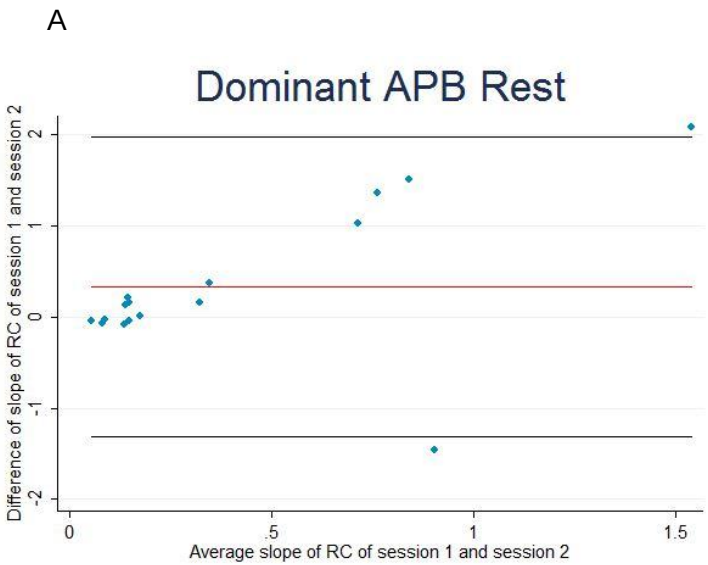


Figure 86 A. Bland-Altman plot of the slope of the RC of the dominant APB at rest, n=16

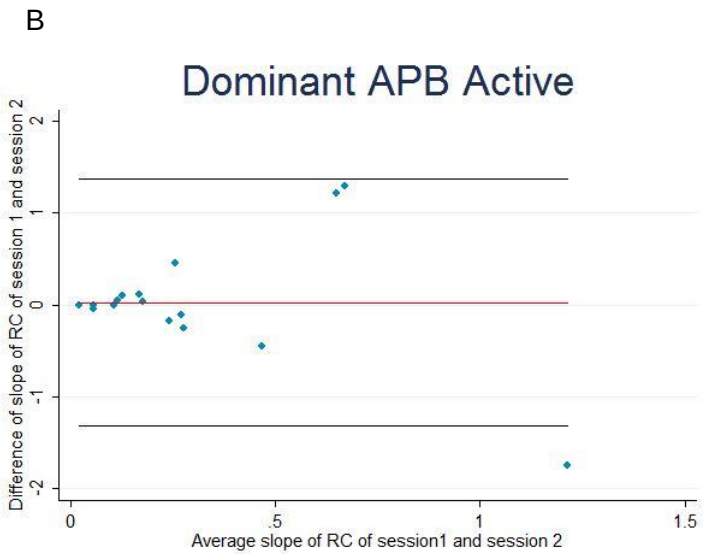


Figure 86 B. Bland-Altman plot of the slope of the RC of the dominant APB during active conditions, n=16

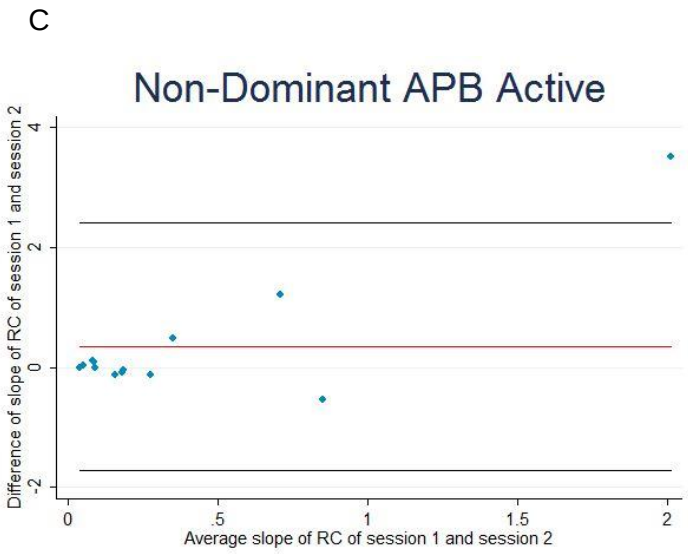


Figure 86 C. Bland-Altman plot of the slope of the RC of the non-dominant APB during active conditions, n=13

Figure 86 A, B, & C - Bland-Altman plots of the slope of the RC of the APB during resting (A) and active conditions (B, C) during 20% MVC calculated individually for each participant at each session. The x axis is the average slope of session 1 and session 2 plotted against the difference in the slope of session 1 minus session 2. The red line is the mean difference in slope of session 1 and session 2. Plots A and B exhibit a potential linear association between the magntidue of the slope and agreement between sessions. Plot C demonstrates a trend toward systematic error such that the second session demonstrates a greater slope Note the different scales of plots A and B compared to plot C. RC=recruitment curve, APB=abductor pollicis brevis. RMT=resting motor threshold, AMT=active motor threshold

Appendix 19: Ethical Approval forms for: “The test-retest reliability of TMS measures of corticospinal pathway excitability early after stroke”

NHS
Health Research Authority

NRES Committee East of England - Norfolk
Nottingham REC Centre
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Tel: 0115 8839436

07 October 2013

Professor Valerie M Pomeroy
Professor of Neurorehabilitation
University of East Anglia
Queen's Building
University of East Anglia
Norwich
NR31 9HL

Dear Professor Pomeroy

Study title:	**Clinical efficacy of functional strength training for upper limb motor recovery early after stroke: neural correlates and prognostic indicators**
REC reference:	**11/EE/0524**
Protocol number:	**1.0**
Amendment number:	**3.0**
Amendment date:	**30 August 2013**
IRAS project ID:	**79063**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Email conversation	Email from Andrew Walker to Norfolk REC	26 July 2013
Protocol	4.0	30 August 2013
Participant Consent Form: Supplementary Assessment	1.0	30 August 2013

Participant Information Sheet: Supplementary Assessment	1.0	30 August 2013
Covering Letter	Letter from Andrew A Walker	09 September 2013
Notice of Substantial Amendment (non-CTIMPs)	79063/498524/13/841/20907	30 August 2013

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

11/EE/0524:	**Please quote this number on all correspondence**

Yours sincerely

Dr Michael Sheldon
Chair

E-mail: NRESCommittee.EastofEngland-Norfolk@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Miss Clare Symms, NHS Norfolk*
Mrs Sue Steel

NRES Committee East of England – Norfolk

Committee Members in Correspondence

Name	*Profession*	*Capacity*
Dr Michael Sheldon	Retired Clinical Psychologist	Lay
Dr Robert Stone	General Practitioner	Expert

Norfolk Community Health and Care NHS Trust

Appendix 20: Participant information Sheet and Consent Form: "Test-retest reliability of TMS Measures of Corticospinal Pathway Early After Stroke"

FAST INdICATE

Functional Strength Training for upper limb recovery after stroke

Supplementary Brain-Muscle Connectivity Assessment Participant Information Form

This document is associated with the study protocol version 4.0 30 August 2013.

An invitation to you

We would like to invite you to take part in a supplementary assessment of the brain-muscle connection, identical to the one you had at the baseline assessment. Before you decide **we would like you to understand why the research is being done** and **what it would involve for you**. One of our team will go through the information sheet with you and answer any questions you have. This will take around 10 minutes.

Talk to others about the supplementary assessment if you wish.

Part 1 gives you the purpose of this supplementary assessment and what will happen if you take part.

Part 2 gives you more detailed information about the conduct of the supplementary assessment.

We are here to help. Ask us if there is anything that is not clear**. Pages 11 and 12** have the names and contact details of **people who can help**.

Part 1

What is the purpose of this additional research?

After stroke **weakness in the arm and hand** prevents people from doing everyday activities such as writing. Understanding the connection between the brain and the muscles of the arm can improve our understanding of how people recover after a stroke. The purpose of this supplementary assessment is to determine the reliability (a measure of how much the connection may change from day to day) of the connection between your brain and muscles early after a stroke.

The **aim** of the is research is to find out **the reliability of the brain-muscle connectivity early after stroke**

Why have I been invited?

We are looking for people who have had a stroke, are participating in the FAST INdICATE trial in Norfolk, and are suitable to receive Transcranial Magnetic Stimulation (TMS). TMS is explained on page 4.

Do I have to take part?

It is up to you to decide to join the supplementary assessment. **We will describe the assessment** and go through this information sheet. If you agree to take part, we will then **ask you to sign a consent form.** You are free to **withdraw from this supplementary research at any time, without giving a reason.** This would **not affect** the standard of **the care you receive or your involvement in the FAST INdICATE research.**

If you are **unable to write or hold a pen** (either **due to the effects of your stroke** or for **another reason**) you can **choose** an **independent person** or if you would prefer, an independent person will be **found for you**. The independent person may be a **member of your medical team**, **a family member** or **friend**. When we use the word independent we mean a **person who is not a member of the research team or a person who cannot be influenced** by the research team. **This person will write on a consent form for you** as **you verbally agree** to take part. This

independent person **cannot decide for you** that will take part and **you will not be asked or made to do anything you do not want to do**.

What will happen if I decide to take part?

- There will be a **supplementary assessment** between 1-3 days following your baseline assessment. The supplementary assessment which will be identical to the one you have already completed.

Will I stop getting any treatment?

If you take part in the research, **you will still receive all the treatment that you would receive if you did not take part**.

What will I have to do?

- If you decide to take part you will have one extra brain-muscle connectivity session using TMS.
- The supplementary assessment will be identical to the one you had at baseline, and will be between 1-3 days following your baseline brain-muscle connectivity assessment.
- The supplementary assessment will last approximately 40 minutes.
- The assessment will take place at either an NHS in-patient area or in the rehabilitation research facility at the University of East Anglia.

What does the supplementary assessment involve?

The assessment involves the use TMS to assess the: **the connection between your brain and the muscles in your weaker arm and hand.**

- **Transcranial Magnetic Stimulation (TMS)**

  This assessment involves the use of a device for producing pain-free stimulation of the areas of the brain that control movement. In response to this stimulation, muscles of the body generate a natural brief burst of activity (a contraction). This muscle activity can be recorded from muscles using a method called electromyography (EMG). The examination of the EMG muscle recordings following TMS can provide information on how well signals sent from the brain connect to muscles in the arm and hand. A picture of someone receiving TMS can be found below.

Expenses and Payments

We cannot pay you for participating in the research but **will arrange and pay for any taxi journeys** you may need to take you to and from the assessment. Taking part in the research will not cost you money.

What are the Possible Disadvantages and Risks of Participating?

Before repeating the assessment we will again **ask you questions to ensure it is safe for you to proceed**. If we think that it is not safe for you to proceed then you will not have the assessment.

We will make every effort to minimise any risk to you as we follow a range of safety standards and best practice policies.

Will my taking part in the supplementary assessment be kept confidential?

Yes. We will follow ethical and legal practice guidelines and all information about you will be handled in confidence. The details are included in Part 2.

This completes Part 1.

If this information in Part 1 interests you and you are considering taking part, please read the information in Part 2 before making any decision.

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Part 2

What happens if I don't want to carry on in the supplementary research?

You may withdraw at any time without giving a reason. **Withdrawing from the supplementary assessment will not affect your treatment now or at any time in the future by any healthcare team, or your involvement in the FAST INdICATE research. If you withdraw from the supplementary assessment, any information collected may still be used.**

What if there is a problem?

If you have a **concern** about the supplementary assessment, you should ask to speak to your researcher who will answer any questions or find someone who can. Your researchers contact details can be found on pages 11-12.

If you remain unhappy or wish to complain formally, you can do this through the **NHS Complaints Procedure**. Details can be obtained from http://www.nhs.uk/choiceintheNHS/Rightsandpledges/complaints/Pages/NHScomplaints.aspx

Norfolk Community Health and Care NHS Trust

Alternatively, you could call the Norfolk Community Health and Care NHS Trust Patient Advice and Liaison Services (PALS) on 0800 088 4449.

What if I am harmed?

If something does go wrong and you are harmed during the research assessment there are **no special compensation arrangements**.

If you are harmed due to someone's negligence then you may have grounds for legal action for compensation against the University of East Anglia but you may have to pay your legal costs.

Will anyone else know that I am in the supplementary assessment?

We will inform your medical team that you are taking part.

If we are concerned at any time about your health during your participation in this study **we will report this to someone** in your medical team.

We will not directly inform your GP.

Who is organising the research?

This research is organized by a PhD student as part of a PhD under direct supervision of experienced researchers as well as the Research and Enterprise Services (REN) department at the UEA. The supplementary assessment is led by **Professor Valerie Pomeroy** and managed by **Nick Leavey (the Trial Manager of Fast INdICATE).**

Norfolk Community Health and Care NHS Trust

Will my taking part in the research be kept confidential?

The research team will only have access to information about you that is relevant to the additional assessment. **All information which is collected about you** during the course of the research will be **kept strictly confidential**, and **any information about you will have your name removed** so that you cannot be recognised.

The data will only **be accessed by authorised persons** within the **Research Team** and the **Research and Development Office of the NHS Trusts,** who ensure the quality of the research carried out.

You will use your unique FAST INdICATE **number** for the purpose of **collecting and analysing data**. This means you will remain anonymous.

How will my information be stored?

Data will be **stored securely** in **research office**s during the research and for **1 year** after completion. Long term data is then stored in a **secure area** in the **University of East Anglia for 20 years.** All procedures for **handling, processing, storage** and **destruction of data** are compliant with the Data Protection Act 1998.

All **computer files** will either be stored in a **secure user authenticated area or encrypted** to protect them from unauthorised access**. All the computer files will be anonymous.**

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What will happen to the results?

The results of the supplementary session will be analysed separately from the bigger FAST INdICATE trial; and will contribute to part of a PhD thesis. These results will add to the knowledge of brain-muscle connectivity by determining the reliability of these measures in acute stroke. The results will be **published in academic journals** and shared with colleagues at conferences but individual participants will **not be identifiable**.

Who has reviewed the supplementary assessment?

The **Norfolk Ethics Committee and the University of East Anglia ethics committee** have approved the supplementary assessment. The main research trial will be monitored by a Trial Management Group, a Trial Steering Committee and a Data Monitoring and Ethics Committee. The supplementary TMS data will be monitored by the Norwich Local Management Group. **All these groups put your safety above everything else.**

Norfolk Community Health and Care NHS Trust

Further Information and Contact Details

Kathryn Collins,

PhD Student

Email: **Kathryn.collins@uea.ac.uk**

Supervisors:

Professor Valerie Pomeroy,

Email: **v.pomeroy@uea.ac.uk**

Dr. Niamh Kennedy,

Email: **niamh.kennedy@uea.ac.uk**

If you would prefer you can contact Nick Leavey, the Trial Manager of FAST INdICATE

Nick Leavey

Trial Manager

n.leavey@uea.ac.uk

By telephone: 01603 593899 (this is a private number with a private answering machine that only Nick can access)

By post: Room 1.21, School of Allied Health Professions, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ

Independent Contact Details:

If you wish to discuss this study with **someone who is not involved** in the research then you can contact the **Norfolk Community Health and Care NHS Trust Patient Advice and Liaison Services (PALS) on 0800 088 4449**.

Thank you for taking the time to read this information. If you choose to participate, you will keep a copy of this participant information sheet and the completed consent form.

Consent Form

Date of Visit |__|__|-|__|__|-|__|__|__|__| (DD-MM-YYYY) Participant Initials |__|__|__|

Participant Screening Number |__|__|-|__|__|__|__|

FAST INdICATE

Functional Strength Training for upper limb recovery after stroke

Supplementary Brain-Muscle Connectivity Assessment

Participant Consent Form

Name of Researcher: _____

Name of Participant: _____

NB. If the potential participant is unable to write, please find an independent witness who may complete this form as verbal consent is given by the potential participant. The independent witness should read each of the 5 items to the potential participant and if the participant agrees, the independent witness should initial each of the boxes with his/her own initials.

The purpose of the independent witness is to physically complete this consent form on the instruction of a participant in the instance that the participant cannot do so for him or herself due to a physical inability to hold and or use a pen, or in the instance in which attempting to do so would or appears to cause distress to the participant. The independent witness cannot provide consent on behalf of a participant.

An independent witness must:

- *Not be part of the research team*
- *Not be managed by a member of the research team*

After completion of this form, two photocopies should be made. One photocopy should be provided to the participant and the second photocopy placed in the participant's medical notes. The original hand signed document should be stored in the Investigator Site File.

Date of Visit |__|__|-|__|__|-|__|__|__|__| (DD-MM-YYYY) Participant Initials |__|__|__|

Participant Screening Number |__|__|-|__|__|__|__|

Please ask either the participant or, if appropriate, the independent witness to sign, print their name and date on this form in long format below. Please then countersign, print and date in long format in the spaces below.

Signed (participant): _____

Print Name (Participant): _____

Date : (DD-MM-YYYY) |_|_| ◦|_|_|◦|_|_|_|_|

Or

Signed (Independent witness): _____

Print Name (independent witness): _____

Date: (DD-MM-YYYY) |_|_| ◦|_|_|◦|_|_|_|_|

And

Signed (researcher): _____

Print name (researcher): _____

Date: (DD-MM-YYYY) |_|_| ◦|_|_|◦|_|_|_|_|

Appendix 21: Bland-Altman Plots of Motor Threshold

Figure 87 - Bland-Altman Plots of the Resting Motor Threshold of the Non-Paretic Upper Limb

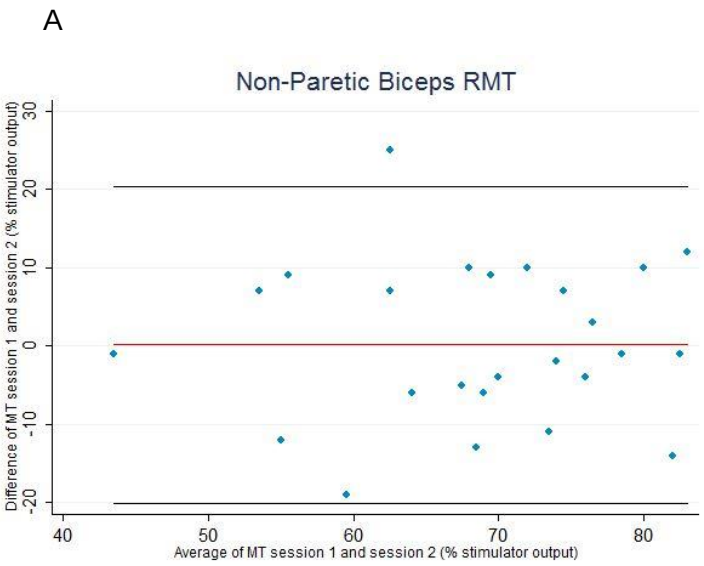


Figure 87A. Bland-Altman plot of RMT of the non-paretic biceps, n=28

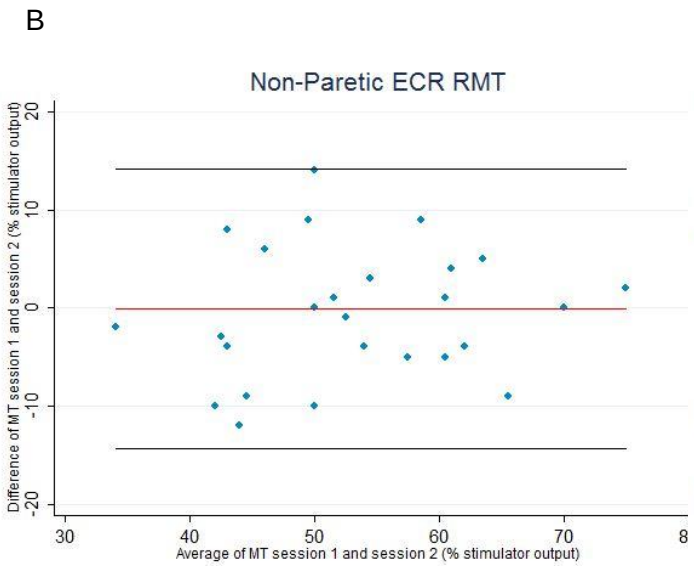


Figure 87B. Bland-Altman plot of RMT of the non-paretic ECR, n=28

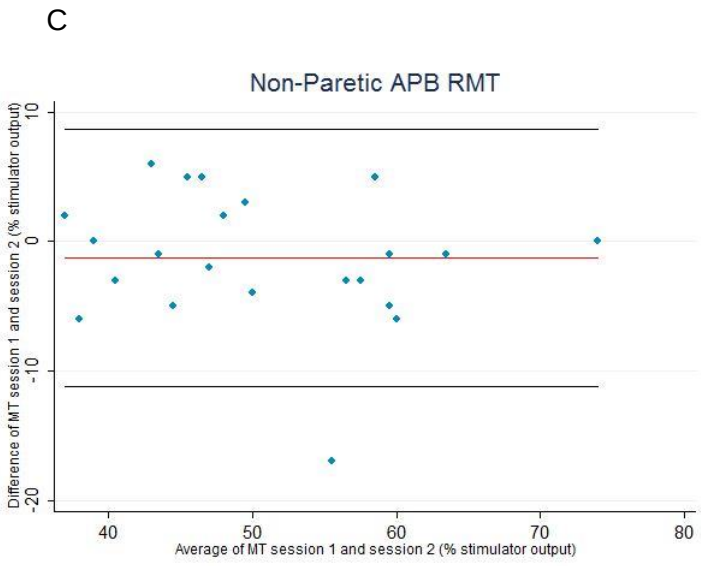


Figure 87C. Bland-Altman plot of RMT of the non-paretic APB, n=27

Figure 87 A, B, & C - Bland-Altman plot of the RMT of the non-paretic biceps, ECR and APB muscles. The x axis is the average RMT of session 1 and session 2 plotted against (y axis) the different in RMT from session 1 minus session 2. The red line is the mean difference in RMT between session 1 and session 2. Plots A, B and C demonstrate random error in agreement etween sesions. Note the different scales of plots A, B, and C. RMT= resting motor threshold, ECR=extensor carpi radialis, APB-abductor pollicis brevis

Figure 88 - Bland-Altman Plots of the Resting Motor Threshold of the Paretic Upper Limb

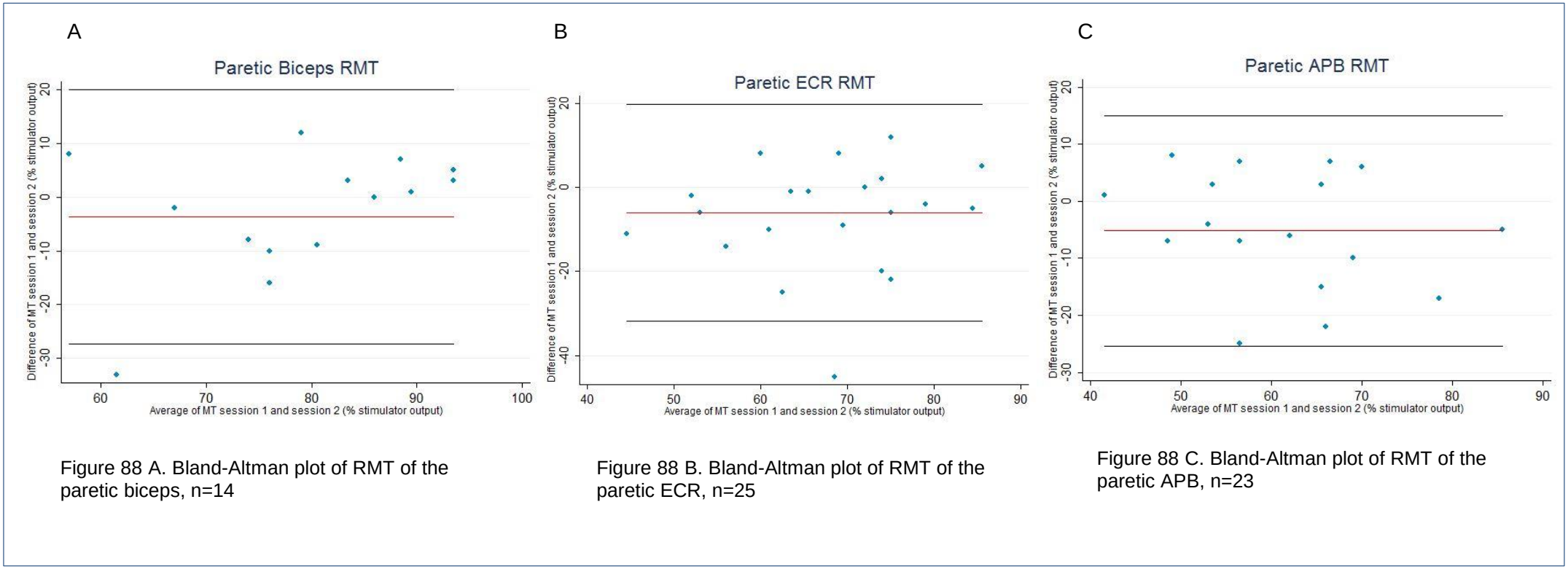


Figure 88 A. Bland-Altman plot of RMT of the paretic biceps, n=14

Figure 88 B. Bland-Altman plot of RMT of the paretic ECR, n=25

Figure 88 C. Bland-Altman plot of RMT of the paretic APB, n=23

Figure 88 A, B, & C - Bland-Altman plot of the RMT of the paretic biceps, ECR and APB muscles. The x axis is the average RMT of session 1 and session 2 plotted against (y axis) the different in RMT from session 1 to session 2. The red line is the mean difference in RMT between session 1 and session 2. Plots A, B and C demonstrate random error in agreement between sessions. Note the different scales of plots A, B, and C. RMT= resting motor threshold, ECR=extensor carpi radialis, APB-abductor pollicis brevis

Figure 89 - Bland-Altman Plots of the Active Motor Threshold Non-Paretic Upper Limb

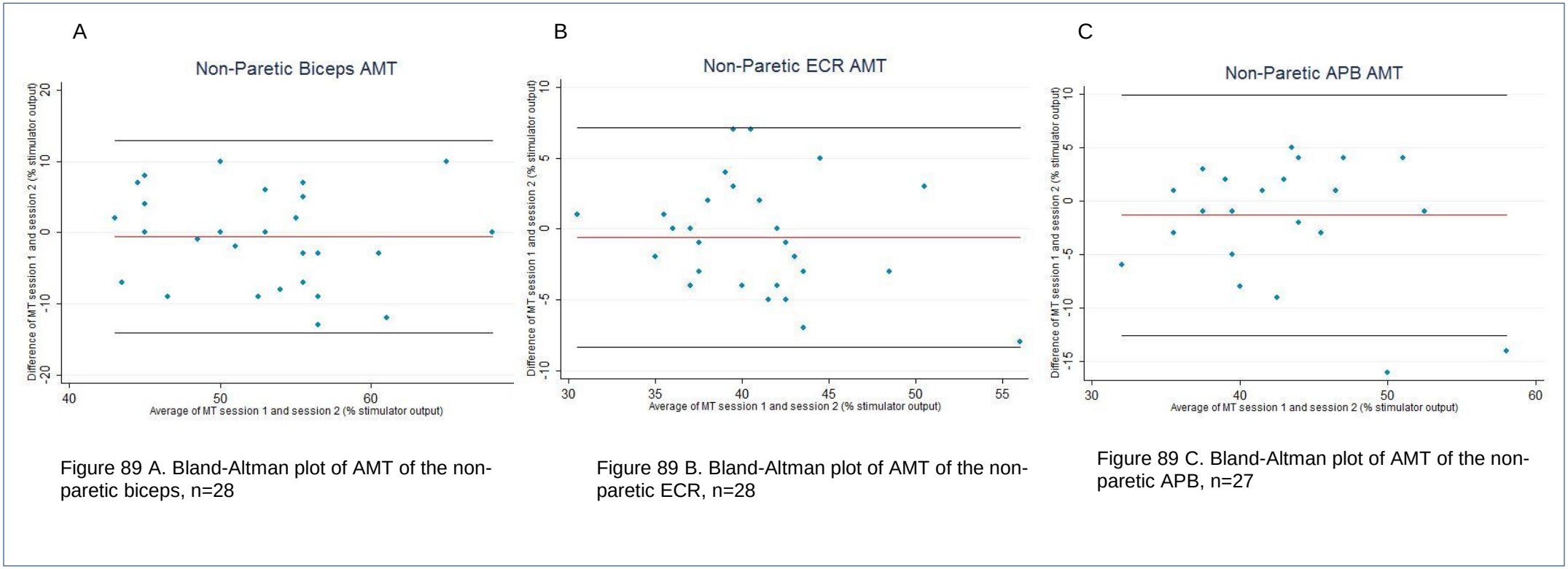


Figure 89 A. Bland-Altman plot of AMT of the non-paretic biceps, n=28

Figure 89 B. Bland-Altman plot of AMT of the non-paretic ECR, n=28

Figure 89 C. Bland-Altman plot of AMT of the non-paretic APB, n=27

Figure 89 A, B, & C - Bland-Altman plot of the AMT of the non-paretic biceps, ECR and APB muscles. The x axis is the average AMT of session 1 and session 2 plotted against (y axis) the different in AMT from session 1 minus session 2. The red line is the mean difference in AMT between session 1 and session 2. Plots A, B and C demonstrate random error in agreement between sessions. Note the different scales of plots A, B, and C. AMT= active motor threshold, ECR=extensor carpi radialis, APB-abductor pollicis brevis

Figure 90 - Bland-Altman Plots of the Active Motor Threshold of the Paretic Upper Limb

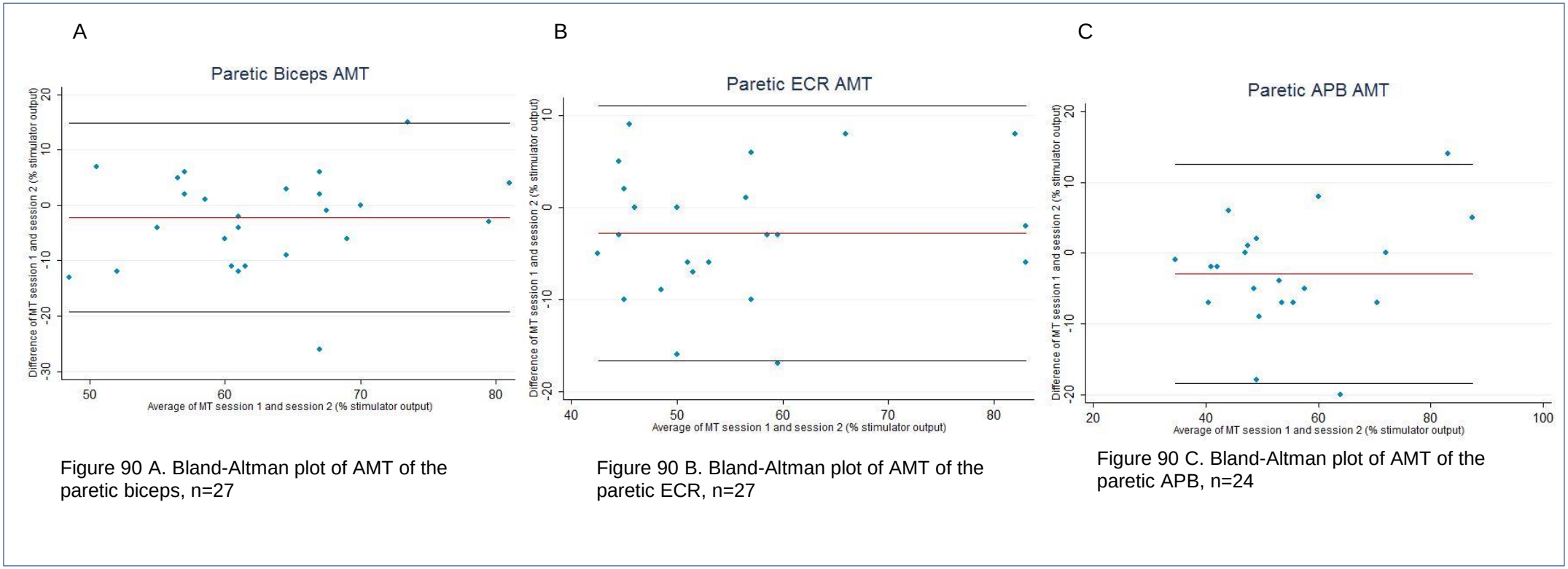


Figure 90 A. Bland-Altman plot of AMT of the paretic biceps, n=27

Figure 90 B. Bland-Altman plot of AMT of the paretic ECR, n=27

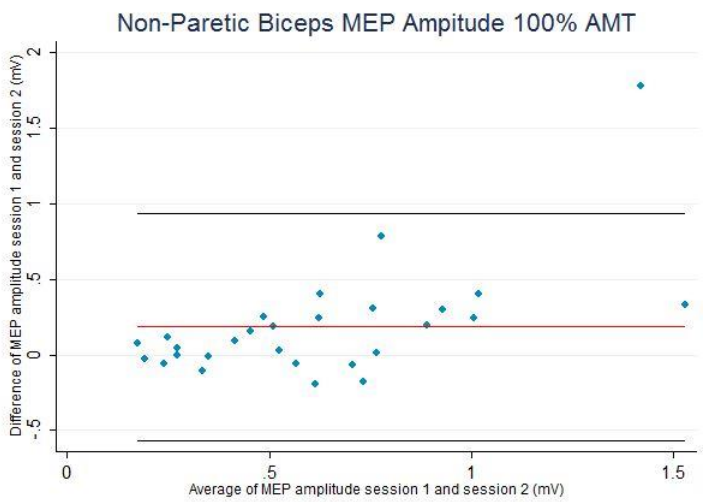
Figure 90 C. Bland-Altman plot of AMT of the paretic APB, n=24

Figure 90 A, B, & C - Bland-Altman plot of the AMT of the paretic biceps, ECR and APB muscles. The x axis is the average AMT of session 1 and session 2 plotted against (y axis) the different in AMT from session 1 minus session 2. The red line is the mean difference in AMT between session 1 and session 2. Plots A, B and C demonstrate random error in agreement between sessions. Note the different scales of plots A, B, and C. AMT= active motor threshold, ECR=extensor carpi radialis, APB-abductor pollicis brevis

Appendix 22: Bland-Altman Plots of the Average MEP Amplitude

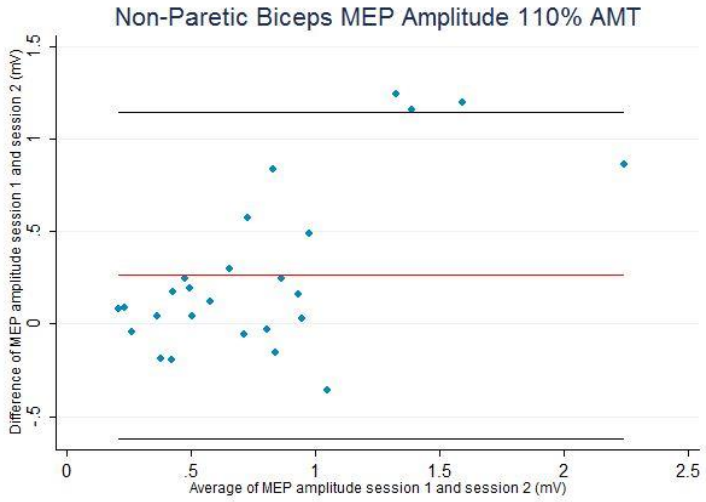
Figure 91 - Bland-Altman Plots of the Average MEP Amplitude of the Non-Paretic Biceps

A



Appendix 22: Bland-Altman Plots of the Average MEP Amplitude

B



Appendix 22: Bland-Altman Plots of the Average MEP Amplitude

Figure 91 A & B - Bland-Altman plot of the average MEP amplitude of the non-paretic biceps muscle at 100%, and 110% of AMT, during slight muscle contraction. The x axis is the average MEP amplitude of session 1 and session 2 plotted against (y axis) the difference in average MEP amplitude from session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A, B demonstrate a potential association between magnitude of EMP amplitude and the difference between sessions. Note the different scales of plots A, B, and C. AMT= active motor threshold MEP=motor evoked potential

Figure 92 - Bland-Altman Plots of the Average MEP Amplitude of the Non-Paretic Biceps

A

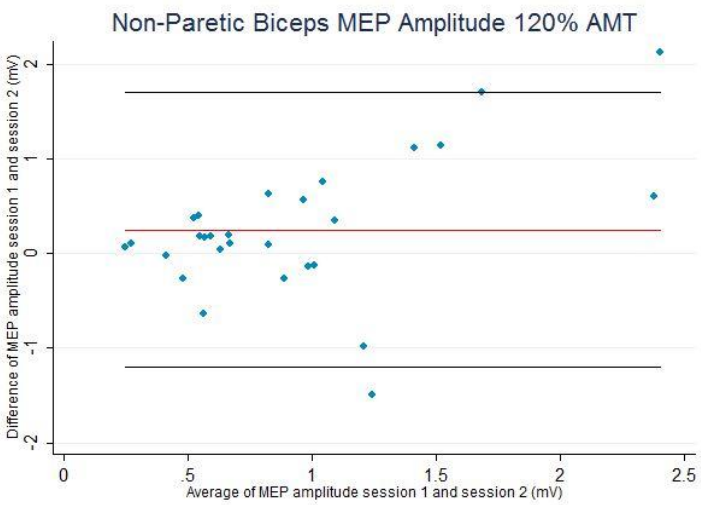


Figure 92 A. Bland-Altman plot of the average MEP amplitude at 120% AMT of the non-paretic biceps, n=28

B

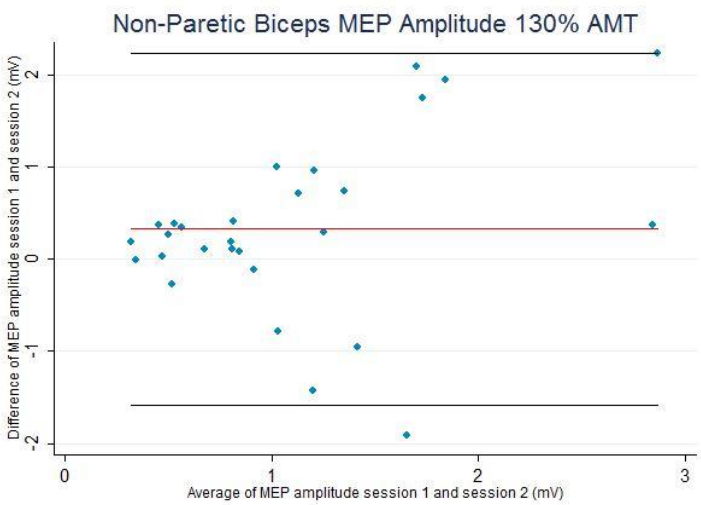


Figure 92 B. Bland-Altman plot of the average MEP amplitude at 130% AMT of the non-paretic biceps, n=28

Figure 92 A & B - Bland-Altman plot of the average MEP amplitude of the non-paretic biceps muscle at 120%, and 130% of AMT, during slight muscle contraction. The x axis is the average MEP amplitude of session 1 and session 2 plotted against (y axis) the difference in average MEP amplitude from session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A, B demonstrate a potential association between the magnitude of MEP amplitude and the difference in measurement between sessions. AMT= active motor threshold MEP=motor evoked potential

Figure 93 - Bland-Altman Plots of the MEP Amplitude of the Non-Paretic ECR Muscle

A

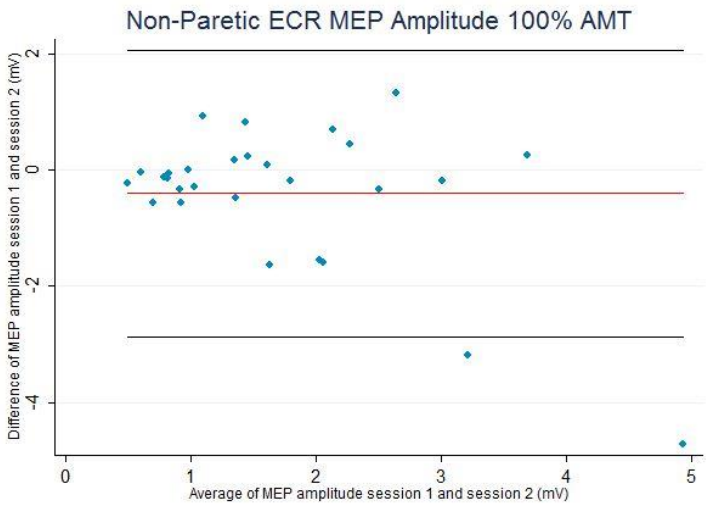


Figure 93 A. Bland-Altman plot of the average MEP amplitude at 100% AMT for the non-paretic ECR, n=28

B

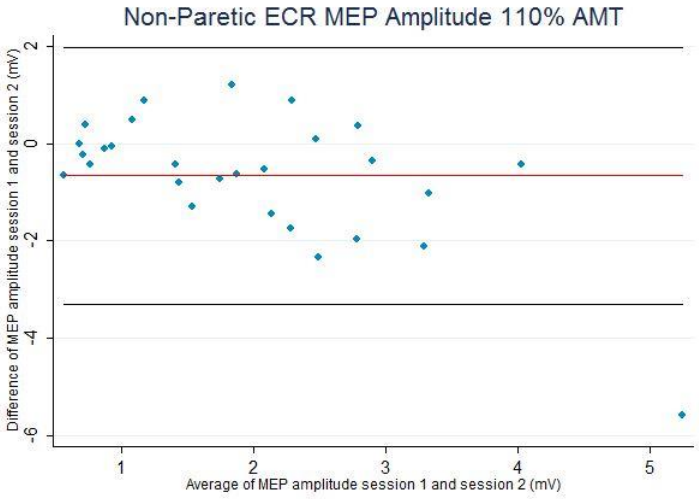


Figure 93 B. Bland-Altman plot of the average MEP amplitude at 110% AMT for the non-paretic ECR, n=28

Figure 93 A & B - Bland-Altman plot of the average MEP amplitude of the non-paretic ECR muscle at 100%, and 110% of AMT, during slight muscle contraction. The x axis is the average MEP amplitude of session 1 and session 2 plotted against (y axis) the difference in average MEP amplitude from session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A, B demonstrate random error in agreement between sessions. AMT= active motor threshold MEP=motor evoked potential ECR=extensor carpi radialis

Figure 94 - Bland-Altman Plots of the MEP Amplitude of the Non-Paretic ECR Muscle

A

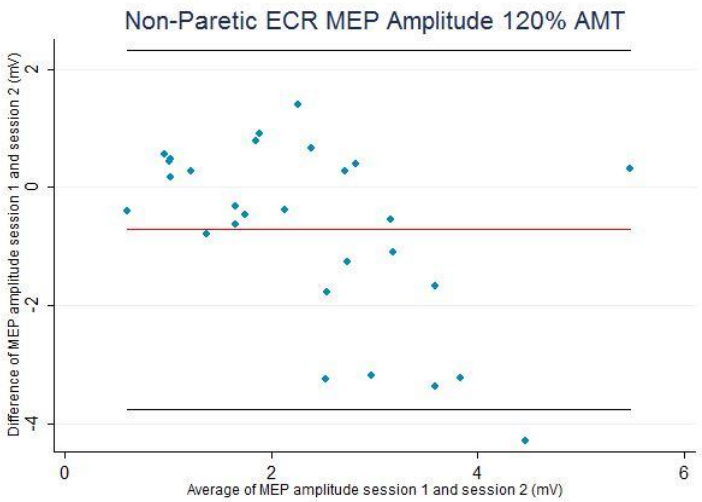


Figure 94 A. Bland-Altman plot of the average MEP amplitude at 120% AMT for the non-paretic ECR, n=28

B

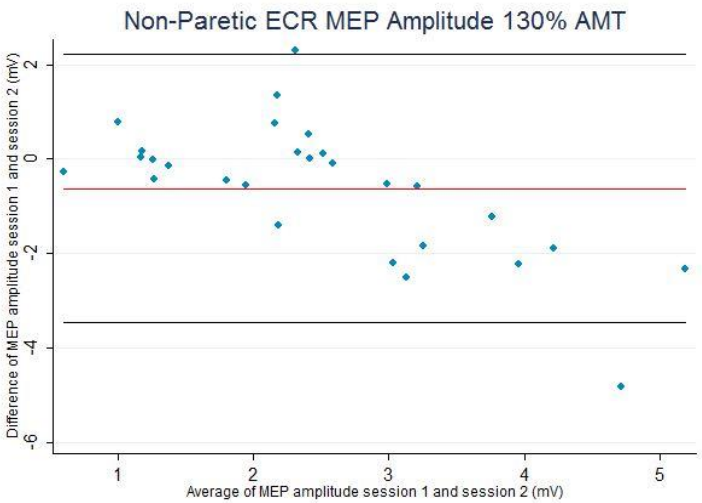


Figure 94 B. Bland-Altman plot of the average MEP amplitude at 130% AMT for the non-paretic ECR, n=28

Figure 94 A & B - Bland-Altman plot of the average MEP amplitude of the non-paretic ECR muscle at 110%, and 120% of AMT, during slight muscle contraction. The x axis is the average MEP amplitude of session 1 and session 2 plotted against (y axis) the difference in average MEP amplitude from session 1 to session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A, B demonstrate random error in agreement between sessions. Note the different scales of plots A and B. AMT= active motor threshold MEP=motor evoked potential, ECR=extensor carpi radialis

Figure 95 - Bland-Altman Plots of the MEP Amplitude of the Non-Paretic APB Muscle

A

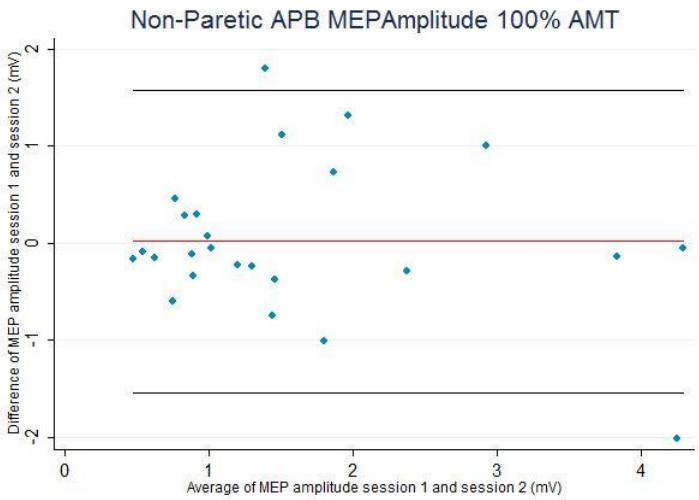


Figure 95 A. Bland-Altman plot of MEP amplitude of the non-paretic APB at 100% AMT, n=27

B

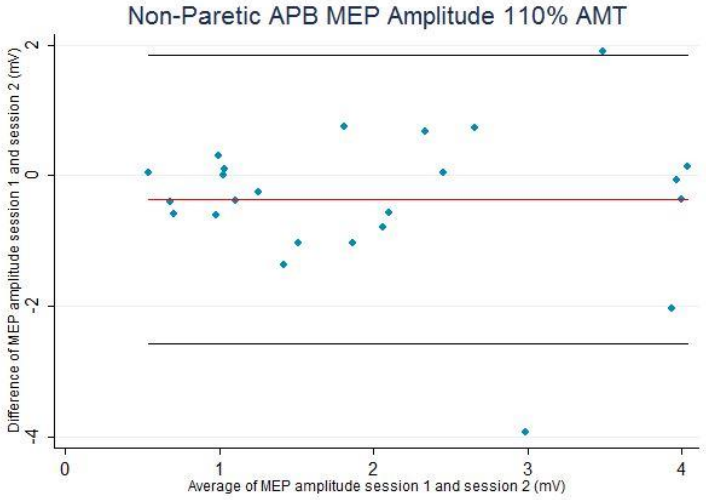


Figure 95 B. Bland-Altman plot of MEP amplitude of the non-paretic APB at 110% AMT, n=27

Figure 95 A & B - Bland-Altman plot of the average MEP amplitude of the non-paretic APB muscle at 100%, and 110% of AMT, during slight muscle contraction. The x axis is the average MEP amplitude of session 1 and session 2 plotted against (y axis) the difference in average MEP amplitude from session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A demonstrates random error in measurement agreement between sessions, plot B demonstrates a potential association between magnitude of MEP amplitude and measurement agreement.. Note the different scales of plots A and B. AMT= active motor threshold MEP=motor evoked potential, APB=abductor pollicis brevis muscle

Figure 96 - Bland-Altman Plots of the MEP Amplitude of the Non-Paretic APB Muscle

A

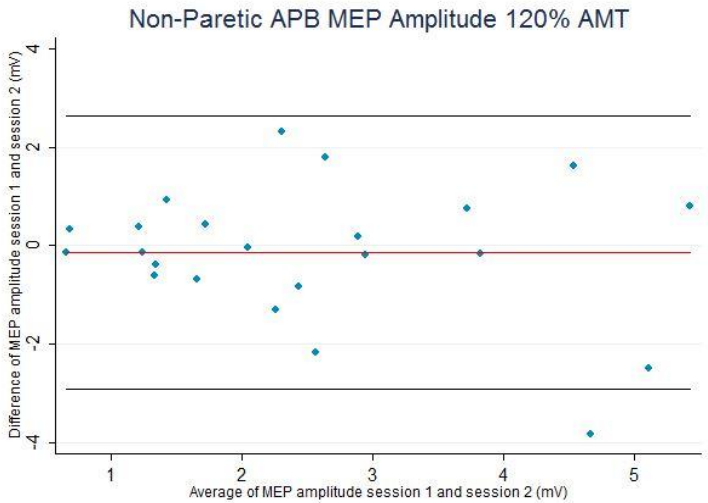


Figure 96 A. Bland-Altman plot of MEP amplitude of the non-paretic APB at 120% AMT, n=27

B

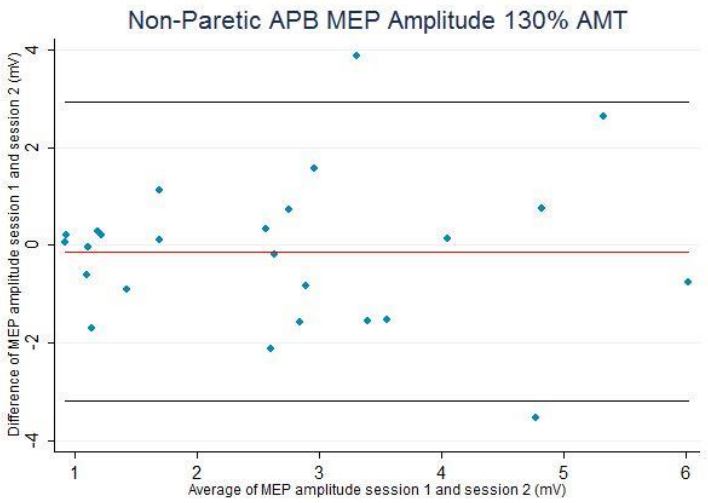


Figure 96 B. Bland-Altman plot of MEP amplitude of the non-paretic APB at 130% AMT, n=27

Figure 96 A & B - Bland-Altman plot of the average MEP amplitude of the non-paretic APB muscle at 120%, and 130% of AMT, during slight muscle contraction. The x axis is the average MEP amplitude of session 1 and session 2 plotted against (y axis) the difference in average MEP amplitude from session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A & B demonstrate random error in agreement between sessions. Note the different scales of plots A and B. AMT= active motor threshold MEP=motor evoked potential, APB=abductor pollicis brevis muscle

Figure 97 - Bland-Altman Plots of the MEP Amplitude of the Paretic Biceps

A

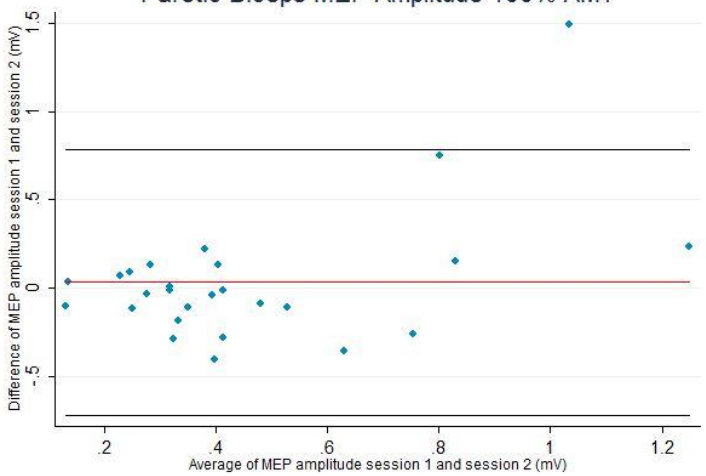


Figure 97 A. Bland-Altman plot of the average MEP amplitude at 100% AMT for the paretic biceps, n=27

B

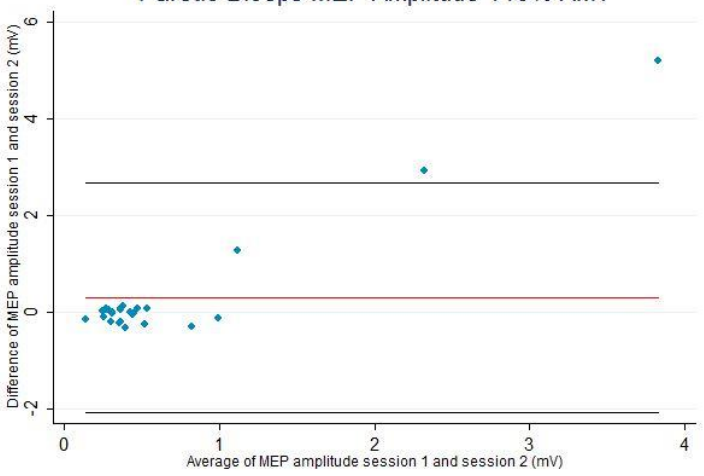


Figure 97 B. Bland-Altman plot of the average MEP amplitude at 110% AMT for the paretic biceps, n=27

Figure 97 A & B - Bland-Altman plot of the average MEP amplitude of the paretic biceps muscle at 100%, and 110% of AMT, during slight muscle contraction. The x axis is the average MEP amplitude of session 1 and session 2 plotted against (y axis) the difference in average MEP amplitude from session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A, B demonstrates a greater number of differences below the mean difference line suggesting greater MEP amplitude at the second session and a potential association between MEP amplitude and measurement agreement. Note the different scales of plots A and B. AMT= active motor threshold MEP=motor evoked potential

Figure 98 - Bland-Altman Plots of the Average MEP for the Paretic Biceps

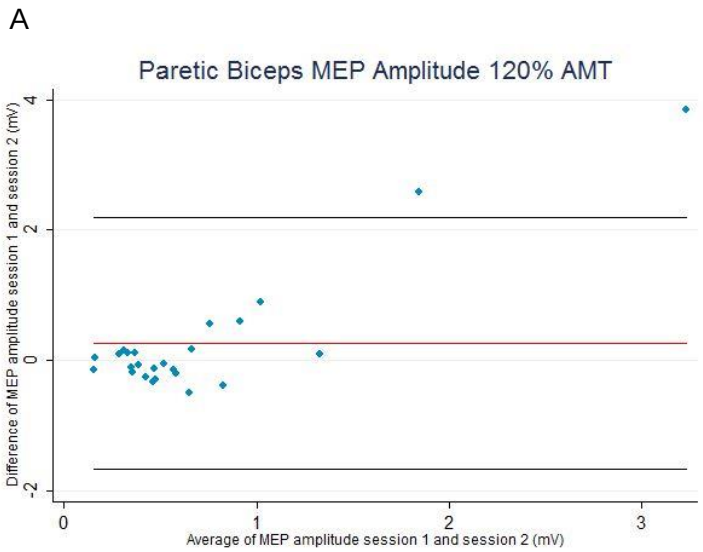


Figure 98 A. Bland-Altman plot of the average MEP amplitude at 120% AMT for the paretic biceps, n=27

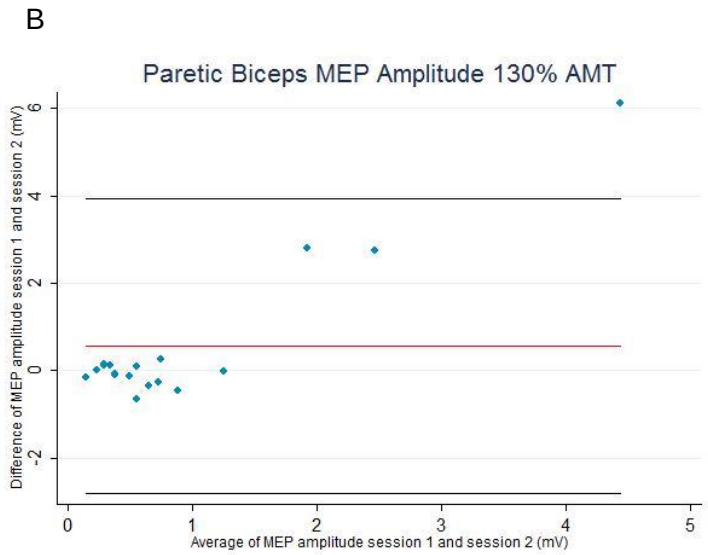


Figure 98 B. Bland-Altman plot of the average MEP amplitude at 130% AMT for the paretic biceps, n=23

Figure 98 A & B - Bland-Altman plot of the average MEP amplitude of the paretic biceps muscle at 120%, and 130% of AMT, during slight muscle contraction. The x axis is the average MEP amplitude of session 1 and session 2 plotted against (y axis) the difference in average MEP amplitude from session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A, B demonstrate a greater number of differences between sessions fall below the mean difference line suggesting greater amplitude at session two as well as a potential association between MEP amplitude and measurement agreement. Note the different scales of plots A and B. AMT= active motor threshold, MEP=motor evoked potential

Figure 99 - Bland-Altman Plots of the Average MEP Amplitude of the Paretic ECR

A

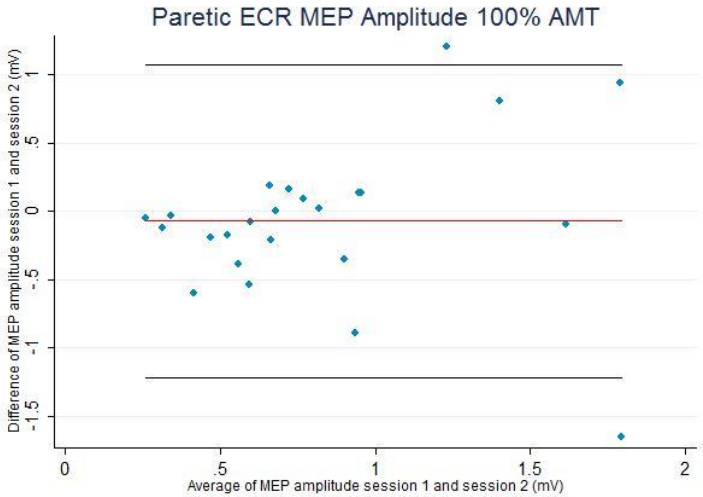


Figure 99 A. Bland-Altman plot of the average MEP amplitude at 100% AMT of the paretic ECR, n=23

B

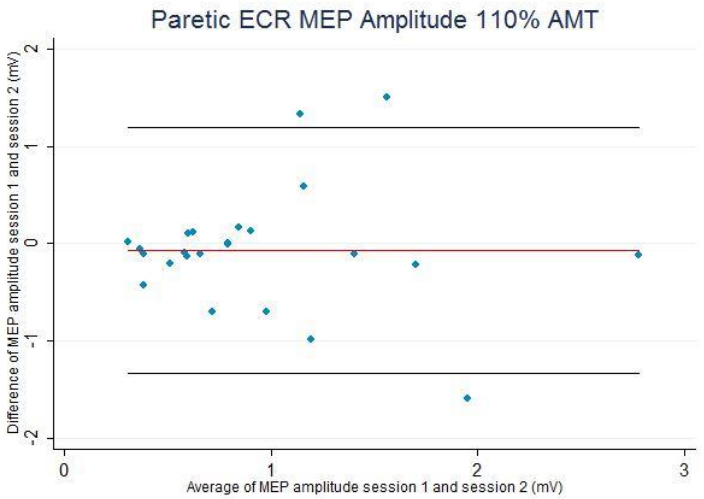


Figure 99 A. Bland-Altman plot of the average MEP amplitude at 110% AMT of the paretic ECR, n=25

Figure 99 A & B - Bland-Altman plot of the average MEP amplitude of the paretic ECR muscle at 100%, and 110% of AMT, during slight muscle contraction. The x axis is the average MEP amplitude of session 1 and session 2 plotted against (y axis) the difference in average MEP amplitude from session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A, B demonstrate a potential association between MEP amplitude and measurement agreement. Note the different scales of plots A and B. AMT= active motor threshold MEP=motor evoked potential, ECR=extensor carpi radialis muscle

Figure 100 - Bland-Altman Plots of the Average MEP Amplitude of the Paretic ECR

A

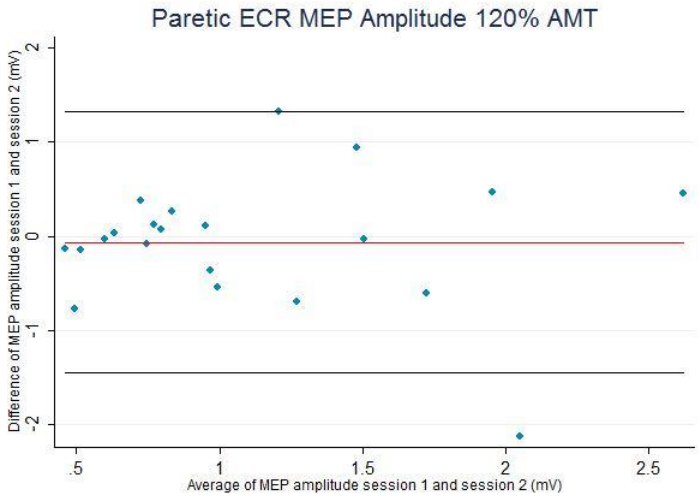


Figure 100 A. Bland-Altman plot of the average MEP amplitude of the paretic ECR at 120% AMT, n=23

B

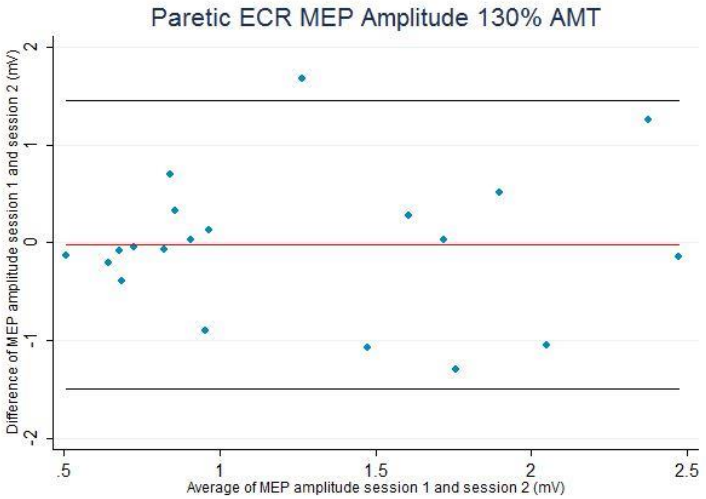


Figure 100 A. Bland-Altman plot of the average MEP amplitude of the paretic ECR at 130% AMT, n=22

Figure 100 A & B - Bland-Altman plot of the average MEP amplitude of the paretic ECR muscle at 120%, and 130% of AMT, during slight muscle contraction. The x axis is the average MEP amplitude of session 1 and session 2 plotted against (y axis) the difference in average MEP amplitude from session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A, B demonstrate random error in agreement between sessions. Note the different scales of plots A and B. AMT= active motor threshold MEP=motor evoked potential, ECR=extensor carpi radialis

Figure 101 - Bland-Altman Plots of the Average MEP Amplitude of the Paretic APB Muscle

A

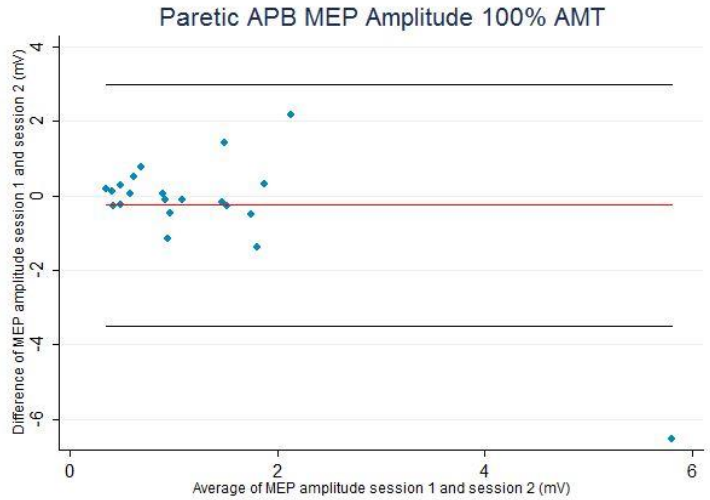


Figure 101 A. Bland-Altman plot of the average MEP amplitude of MEP of paretic APB at 100% AMT, n=24

B

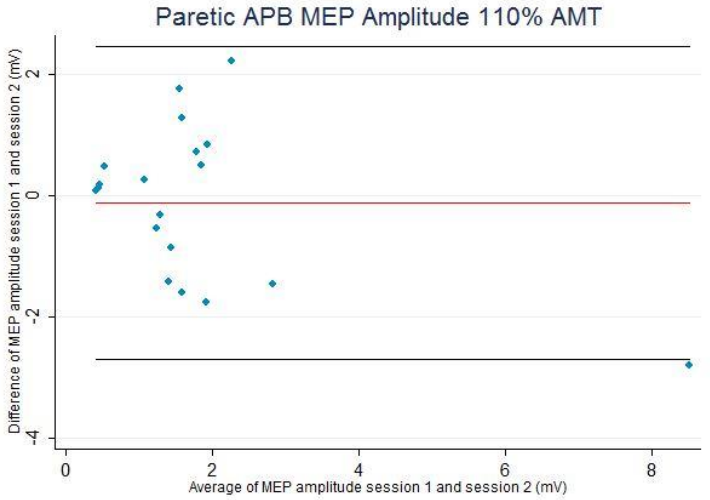


Figure 101 A. Bland-Altman plot of the average MEP amplitude of MEP of paretic APB at 110% AMT, n=24

Figure 101 A & B - Bland-Altman plot of the average MEP amplitude of the paretic APB muscle at 110%, and 120% of AMT, during slight muscle contraction. The x axis is the average MEP amplitude of session 1 and session 2 plotted against (y axis) the difference in average MEP amplitude from session 1minussession 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A, B demonstrate random a potential association between magnitude of MEP amplitude and measurement agreement. Note the different scales of plots A and B. AMT= active motor threshold MEP=motor evoked potential, APB=abductor pollicis brevis muscle

Figure 102 - Bland-Altman Plots of the Average MEP Amplitude of the Paretic APB Muscle

A

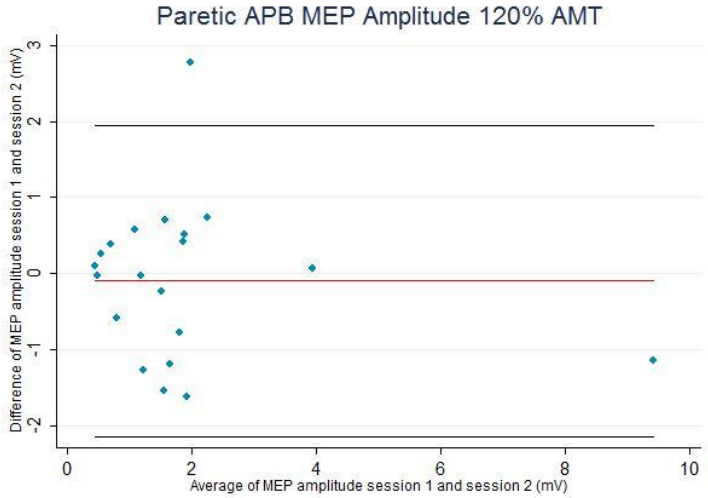


Figure 102 A. Bland-Altman plot of the average MEP amplitude of MEP of paretic APB at 120% AMT, n=21

B

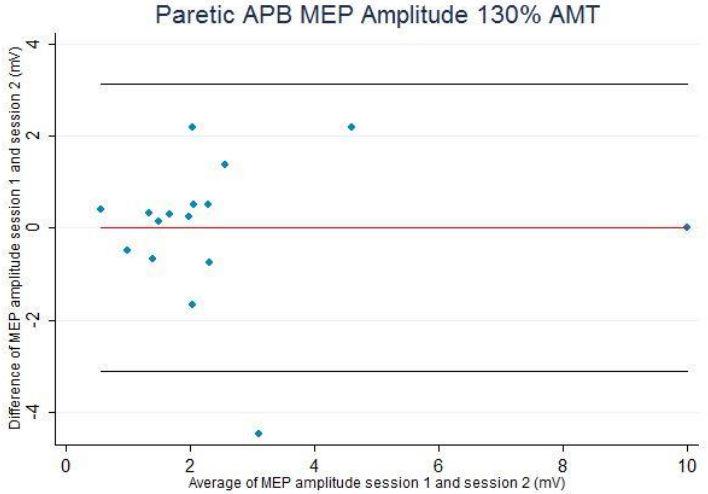


Figure 102 A. Bland-Altman plot of the average MEP amplitude of MEP of paretic APB at 130% AMT, n=19

Figure 102 A & B - Bland-Altman plot of the average MEP amplitude of the paretic APB muscle at 120%, and 130% of AMT, during slight muscle contraction. The x axis is the average MEP amplitude of session 1 and session 2 plotted against (y axis) the difference in average MEP amplitude from session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A, B demonstrate a potential association between MEP amplitude and the difference between sessions. AMT= active motor threshold MEP=motor evoked potential, APB=abductor pollicis brevis muscle

Appendix 23 Bland-Altman Plots of MEP Max Amplitude

Figure 103- Bland-Altman Plots of the MEP Max Amplitude of the non-paretic upper limb

A.

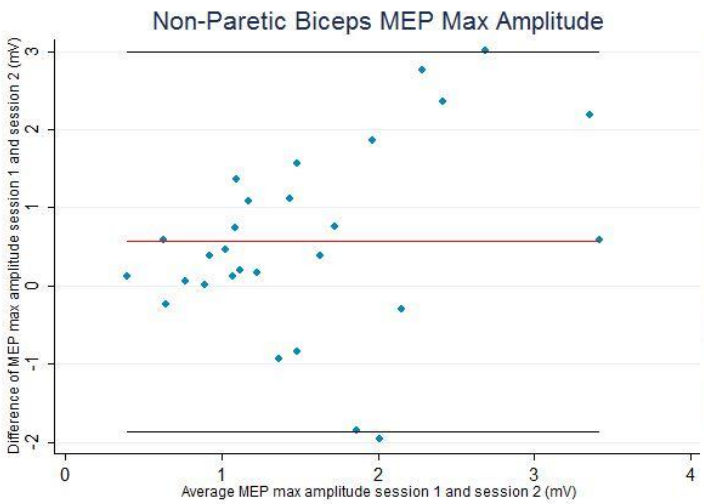


Figure 103 A Bland-Altman plot of the non-paretic biceps MEP max amplitude, n=28

B.

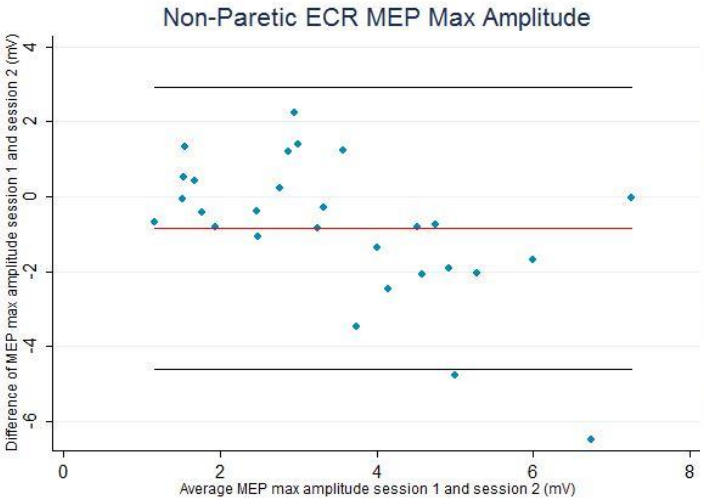


Figure 103 B Bland-Altman plot of the non-paretic ECR MEP max amplitude, n=25

C.

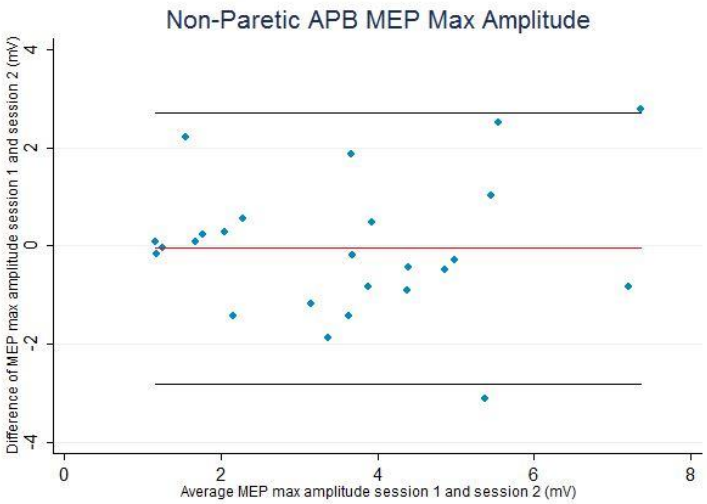


Figure 103 C Bland-Altman plot of the non-paretic APB MEP max amplitude, n=27

Figure 103 A,B,C Bland-Altman plots of the non-paretic MEP max amplitude of the A) biceps, B) ECR and C) APB assessed during slight muscle contraction. The x axis is the average MEP max amplitude of session 1 and session 2 plotted against (y axis) the difference in average MEP max amplitude from session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A, B demonstrate a potential association between MEP max amplitude and the difference between sessions. MEP=motor evoked potential, ECR=extensor carpi radialis, APB=abductor pollicis brevis muscle

Figure 104- Bland-Altman Plots of the MEP Max Amplitude of the Paretic Upper Limb

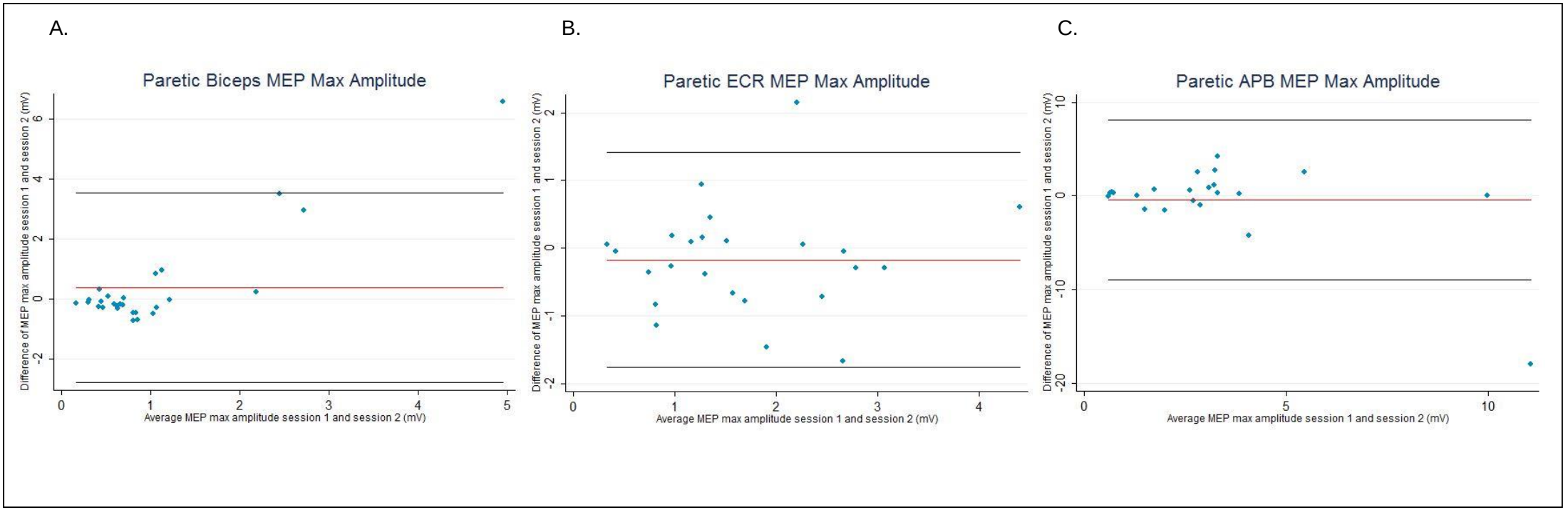


Figure 104 A. Bland-Altman plot of the paretic

*Figure 104*B. Bland-Altman plot of the paretic ECR

*Figure 104*C. Bland-Altman plot of the paretic biceps muscle MEP max amplitude, n=27

muscle MEP max amplitude, n=25

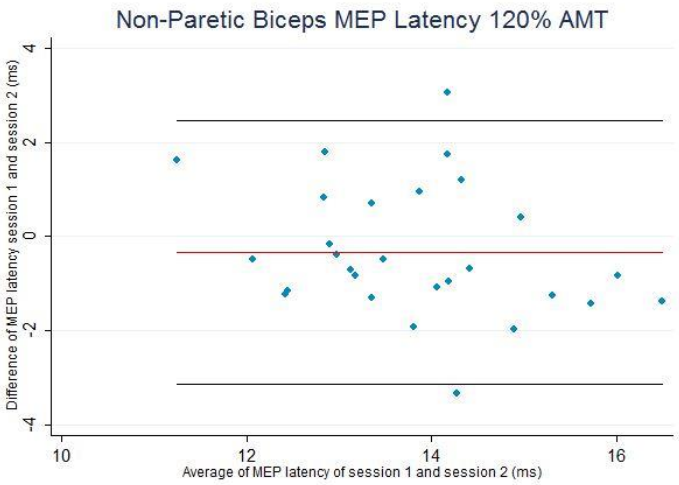
APB muscle MEP max amplitude, n=24

Figure 104A, B, and C - Bland-Altman plots of the paretic MEP max amplitude of the A) biceps, B) ECR and C) APB assessed during slight muscle contraction. The x axis is the average MEP max amplitude of session 1 and session 2 plotted against (y axis) the difference in average MEP max amplitude from session 1 minus session 2. The red line is the mean difference in average MEP amplitude between session 1 and session 2. Plots A demonstrates a greater number of differences between sessions below the mean difference suggesting greater MEP amplitudes at the second session, as well as a potential association between MEP amplitude and difference between sessions. Plot B demonstrates random error in agreement between sessions. Plot C demonstrates a potential association between MEP max amplitude and the difference between sessions. MEP=motor evoked potential, ECR=extensor carpi radialis, APB=abductor pollicis brevis muscle

Appendix 24: Bland-Altman Plots of MEP Latency

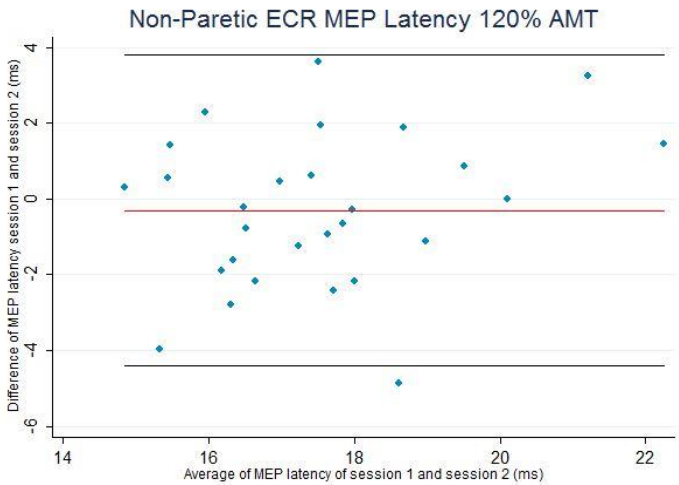
Figure 105 - Bland-Altman Plots of the MEP Latency of the Non-Paretic Limb Assessed at 130% AMT

A



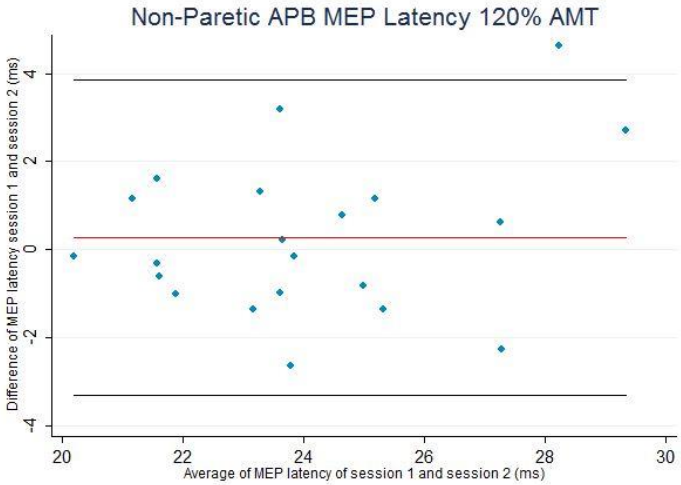
Appendix 24: Bland-Altman Plots of MEP Latency

B



Appendix 24: Bland-Altman Plots of MEP Latency

C



Appendix 24: Bland-Altman Plots of MEP Latency

Figure 105 A, B, & C - Bland-Altman plot of MEP latency of the non-paretic biceps, ECR, and APB muscles assessed at 120% AMT, during slight muscle contraction. The x axis is the latency of session 1 and session 2 plotted against (y axis) the difference in latency from session 1 to session 2. The red line is the mean difference in latency between session 1 and session 2. Plots A, B demonstrate random error as the difference between tests is dispersed above and below the mean difference line. . Note the different scales of plots A and B. AMT= active motor threshold MEP=motor evoked potential, ECR=extensor carpi radialis, APB= abductor pollicis brevis

Figure 106 - Bland-Altman Plots of the MEP Latency of the Paretic Muscles Assessed at 120% AMT

A

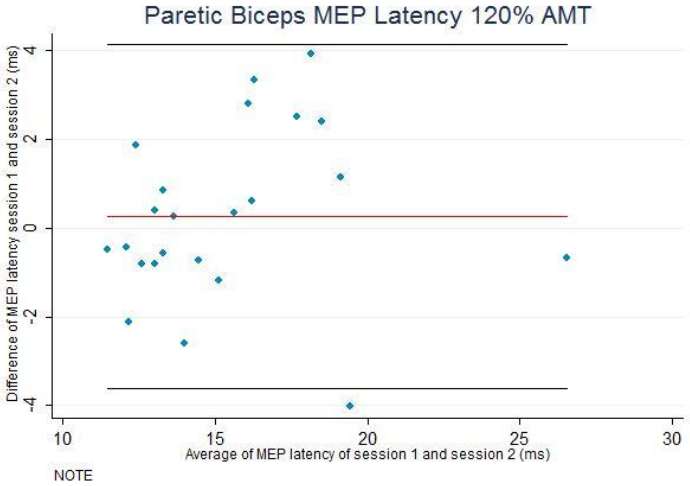


Figure 106 A. Bland-Altman plot of MEP latency of paretic biceps at 120% AMT, n=21

B

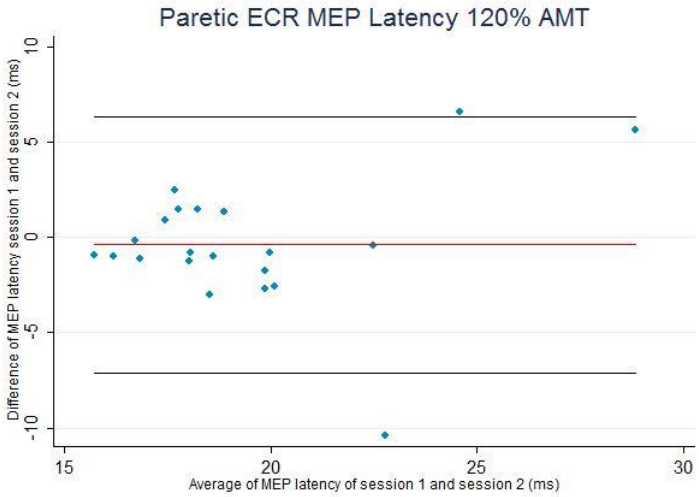


Figure 106 B. Bland-Altman plot of MEP latency of paretic ECR at 120% AMT, n=21

C

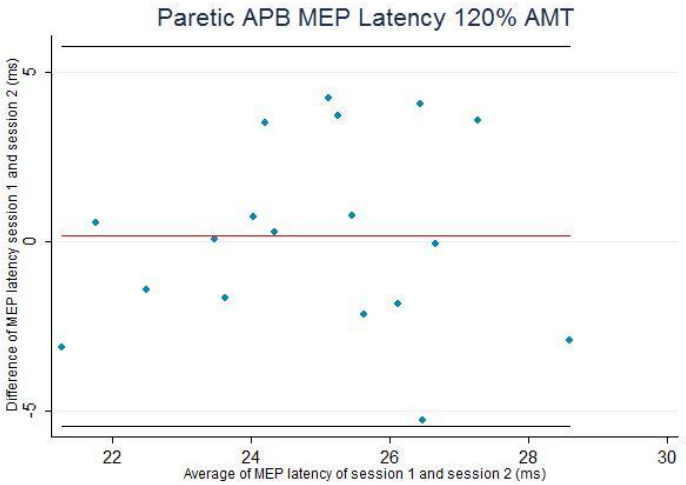


Figure 106 C. Bland-Altman plot of MEP latency of paretic APB at 120% AMT, n=22

Figure 106 A, B, & C - Bland-Altman plot of MEP latency of the non-paretic biceps, ECR, and APB muscles assessed at 120% AMT, during slight muscle contraction. The x axis is the latency of session 1 and session 2 plotted against (y axis) the difference in latency from session 1 to session 2. The red line is the mean difference in latency between session 1 and session 2. Plots A, B demonstrate random error as the difference between tests is dispersed above and below the mean difference line. Note the different scales of plots A and B. AMT= active motor threshold MEP=motor evoked potential, ECR=extensor carpi radialis, APB= abductor pollicis brevis

Figure 107 - Bland-Altman Plots of the MEP Latency of the Non-Paretic Muscles Assessed at 130% AMT

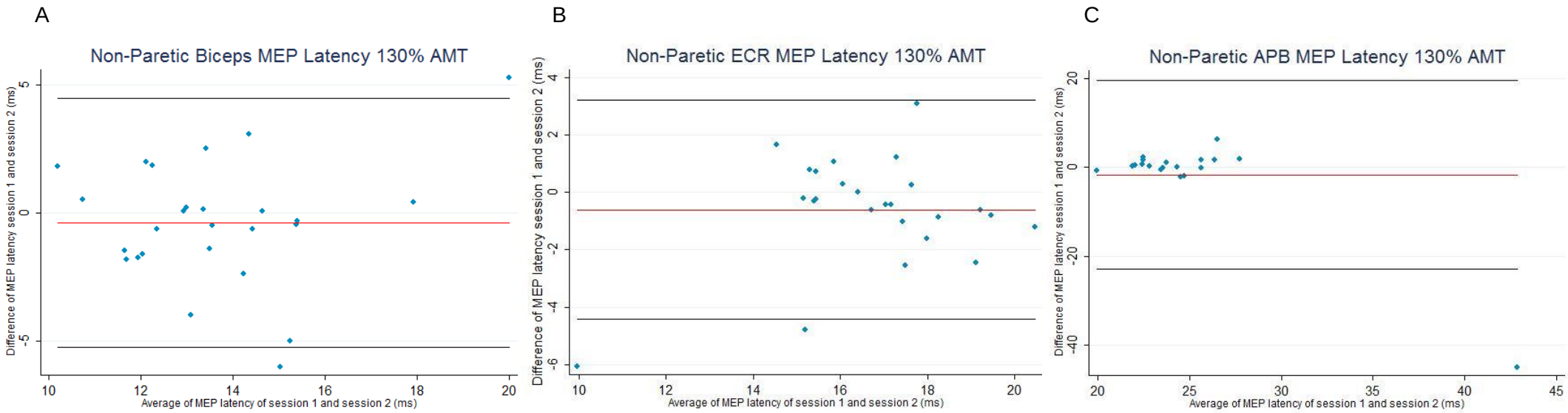


Figure 107A. Bland-Altman plot of MEP latency of 130% AMT of the non-paretic biceps, n=26

Figure 107B. Bland-Altman plot of MEP latency of 130% AMT of the non-paretic ECR, n=26

Figure 107C. Bland-Altman plot of MEP latency of 130% AMT of the non-paretic APB, n=22

Figure 107A, B, & C - Bland-Altman plot of MEP latency of the non-paretic biceps, ECR and APB assessed at 130% AMT, with slight background contraction. The x axis is the MEP latency of session 1 and session 2 plotted against (y axis) the difference in MEP latency from session 1 minus session 2. The red line is the mean difference in MEP latency between session 1 and session 2. Plots A, B, demonstrate random error in agreement between sessions. Plot C demonstrate a greater number of differences above the mean difference line suggesting shorter latency the second session. Note the different scales of plots A, B, and C. AMT= active motor threshold MEP=motor evoked potential, ECR=Extensor carpi radialis muscle, APB=abductor pollicis brevis muscle

Figure 108 - Bland-Altman Plots of the MEP Latency of the Paretic Muscles Assessed at 130% AMT

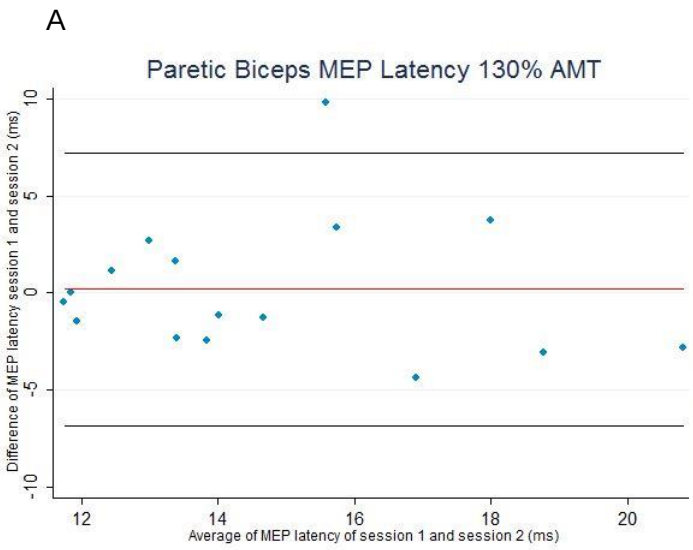


Figure 108A. Bland-Altman plot of MEP latency of 130% AMT of the paretic biceps, n=16

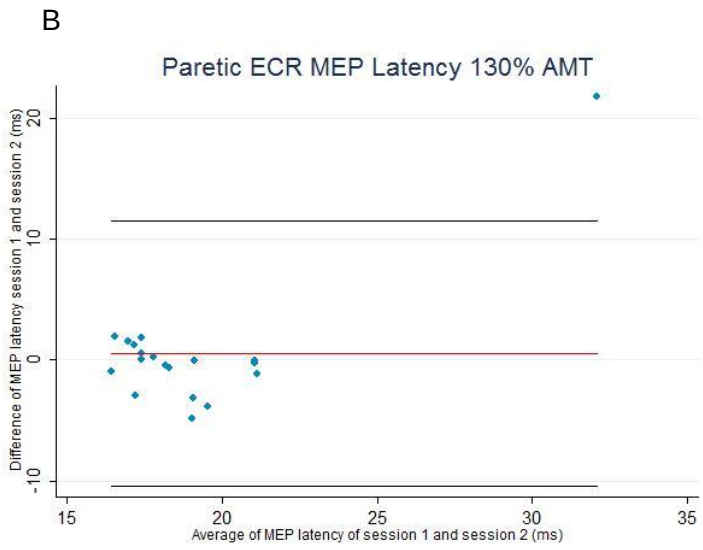


Figure 108B. Bland-Altman plot of MEP latency of 130% AMT of the paretic ECR, n=18

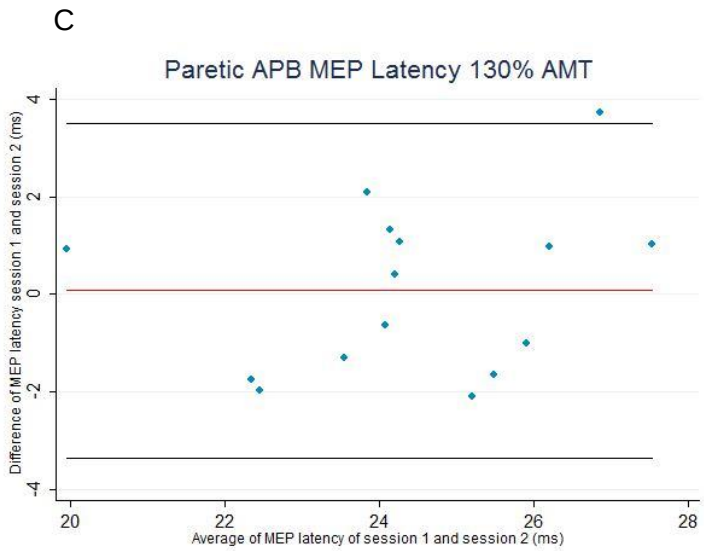
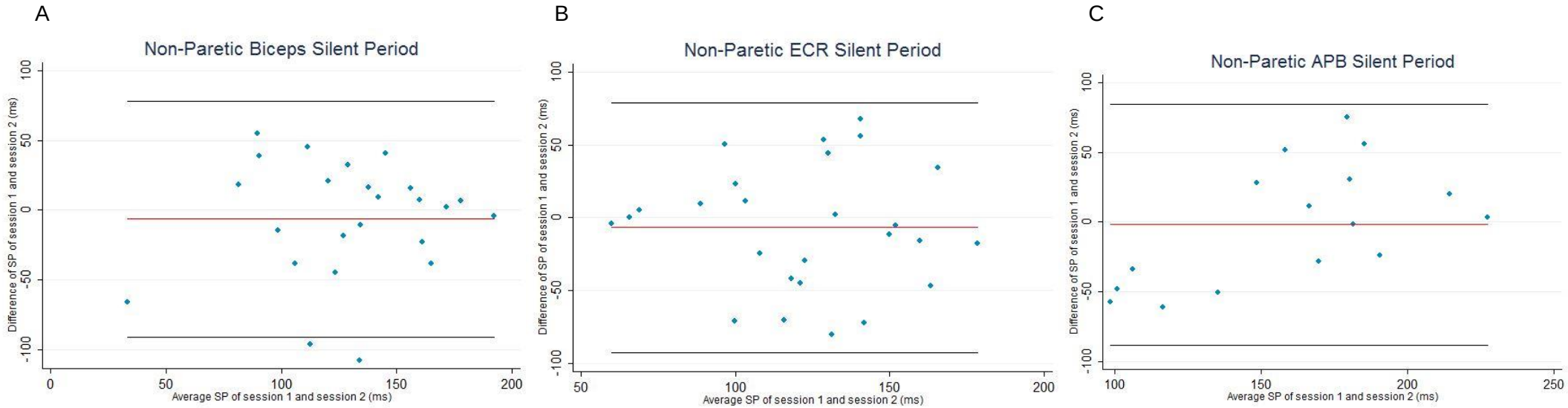


Figure 108C. Bland-Altman plot of MEP latency of 130% AMT of the paretic APB, n=15

Figure 108A, B, & C - Bland-Altman plot of MEP latency of the paretic biceps, ECR and APB assessed at 130% AMT, with slight background contraction. The x axis is the MEP latency of session 1 and session 2 plotted against (y axis) the difference in MEP latency from session 1 to session 2. The red line is the mean difference in MEP latency between session 1minus session 2. Plots A demonstrates a trend towards greater differences with longer latency. Plot B demonstrates a greater number of differences below the mean difference line suggesting longer latency the second session, and Plot C potentially demonstrates an association with magnitude of response and difference between sessions. Note the different scales of plots A, B, and C. AMT= active motor threshold MEP=motor evoked potential, ECR=Extensor carpi radialis muscle, APB=abductor pollicis brevis muscle

Appendix 25 Bland-Altman Plots of the Silent Period

Figure 109 - Bland-Altman Plots of the Silent Period of the Non-Paretic Muscles Assessed at 130% of AMT



Appendix 25 Bland-Altman Plots of the Silent Period

Appendix 25 Bland-Altman Plots of the Silent Period

Appendix 25 Bland-Altman Plots of the Silent Period

Figure 109A, B, & C - Bland-Altman plot of SP of the non-paretic biceps, ECR and APB assessed at 130% AMT, with slight background contraction. The x axis is the SP of session 1 and session 2 plotted against (y axis) the difference in SP from session 1 minus session 2. The red line is the mean difference in MEP latency between sessions. Plots A, B, and C demonstrate random error in agreement between sessions. Note the different scales of plots A, B, and C. SP=silent period, AMT= active motor threshold MEP=motor evoked potential, ECR=Extensor carpi radialis muscle, APB=abductor pollicis brevis muscle

Figure 110 - Bland-Altman Plots of the Silent Period of the Paretic Muscles Assessed at 130% of AMT

A

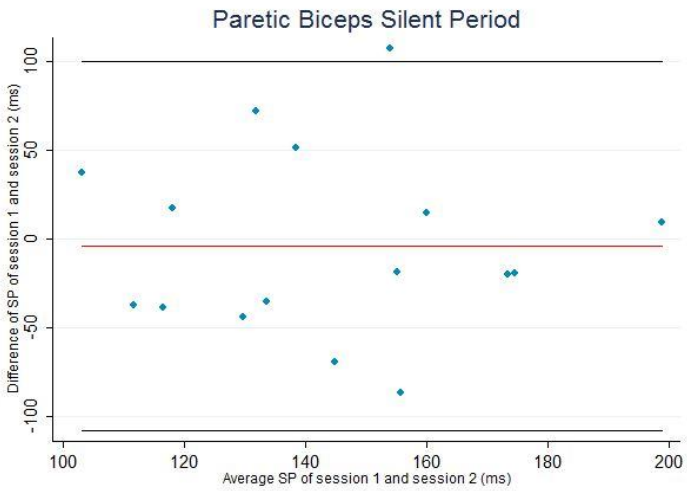


Figure 110A. Bland-Altman plot of SP assessed at 130% AMT of the paretic biceps, n=22

B

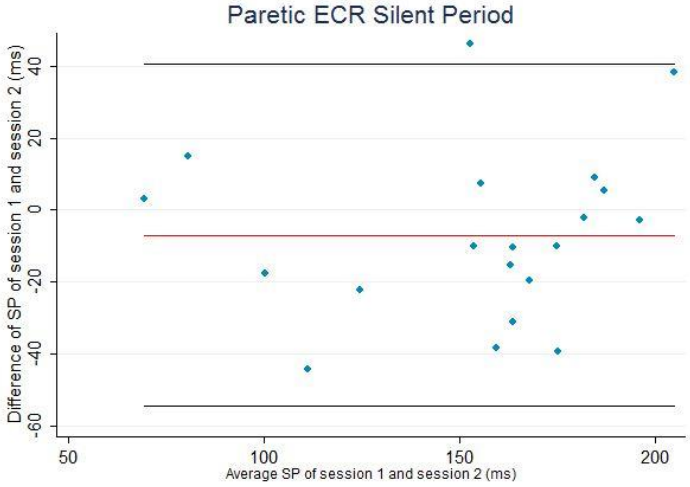


Figure 110B. Bland-Altman plot of SP assessed at 130% AMT of the paretic ECR, n=22

C

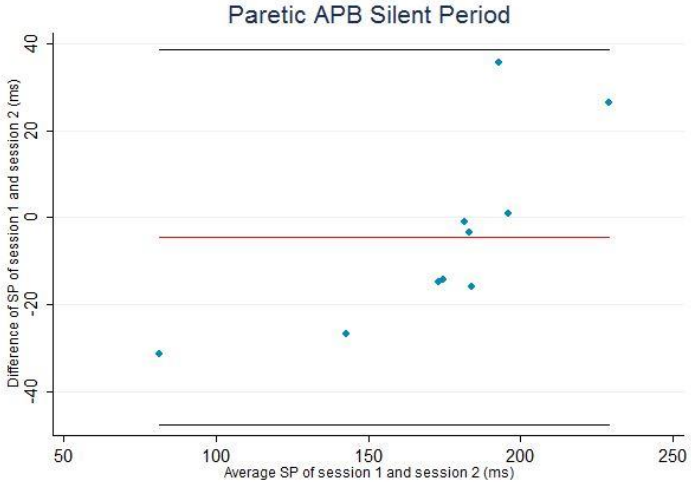


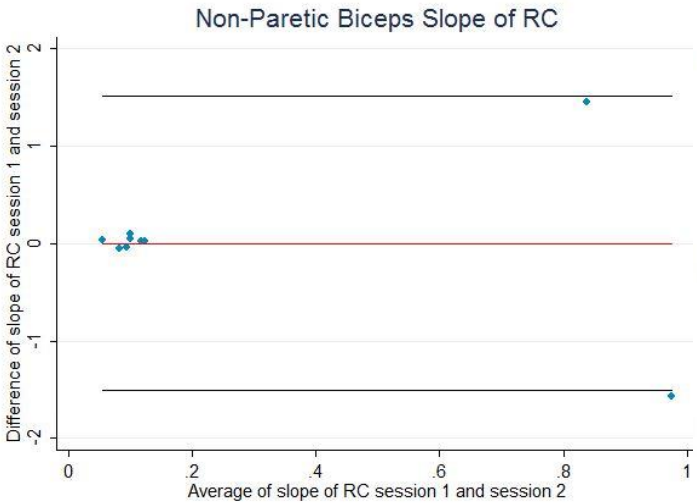
Figure 110C. Bland-Altman plot of SP assessed at 130% AMT of the paretic APB, n=10

Figure 110A, B, & C - Bland-Altman plot of SP of the paretic biceps, ECR and APB assessed at 130% AMT, with slight background contraction. The x axis is the SP of session 1 and session 2 plotted against (y axis) the difference in SP from session 1 minus session 2. The red line is the mean difference in SP between session 1 and session 2. Plots A demonstrates random error, plots B, and C demonstrate a potential association between magnitude of the SP and measurement agreement.. Note the different scales of plots A, B, and C. SP=silent period, AMT= active motor threshold MEP=motor evoked potential, ECR=Extensor carpi radialis muscle, APB=abductor pollicis brevis muscle

Appendix 26: Bland-Altman Plots of the Slope of the Recruitment Curve

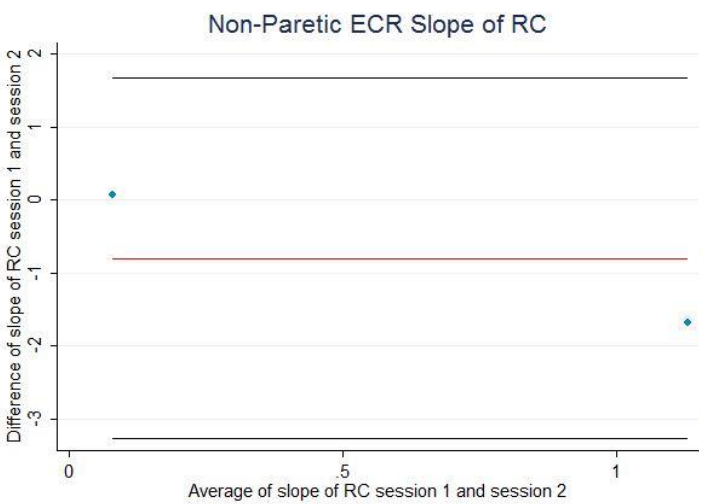
Figure 111 - Bland-Altman Plots of the Slope of the Recruitment Curve of the Non-Paretic Muscles

A



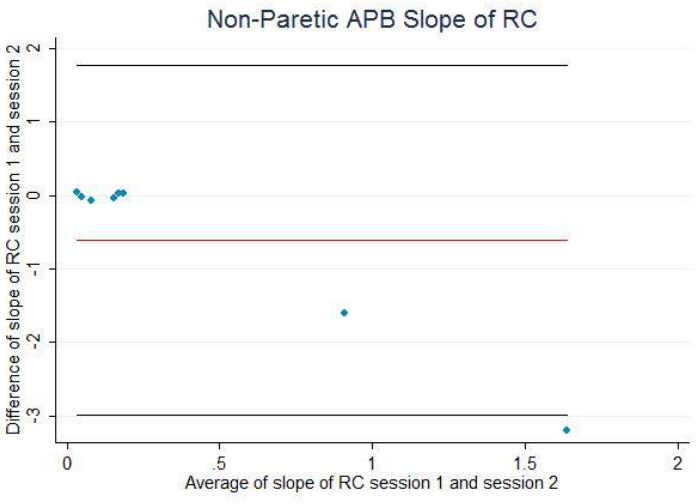
Appendix 26: Bland-Altman Plots of the Slope of the Recruitment Curve

B



Appendix 26: Bland-Altman Plots of the Slope of the Recruitment Curve

C



Appendix 26: Bland-Altman Plots of the Slope of the Recruitment Curve

Figure 111A, B, & C - Bland-Altman plots of the slope of the RC of the non-paretic biceps (A), ECR (B), and APB (C) assessed during slight muscle contraction. The x axis is the average slope of session 1 and session 2 plotted against (y axis) the difference in slope of session 1 minus session 2, the red line is the mean difference line in the slope of session1 an session 1. Plot A demonstrates greater differences between sessions with greater slopes. Plot C demonstrates the slope of the RC was less steep at the second session. Note the different scales of plots A, B, C. RC=recruitment curve, ECR=extensor carpi radilais muscle, APB=abductor pollicis brevis muscle

Figure 112 - Bland-Altman Plots of the Slope of the Recruitment Curve of the Paretic Muscles

A

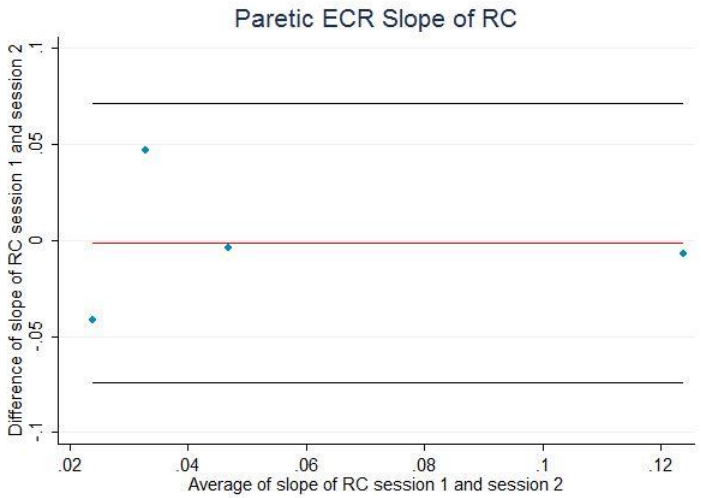


Figure 112A. Bland-Altman plot of the slope of the RC of the paretic ECR, n=4

B

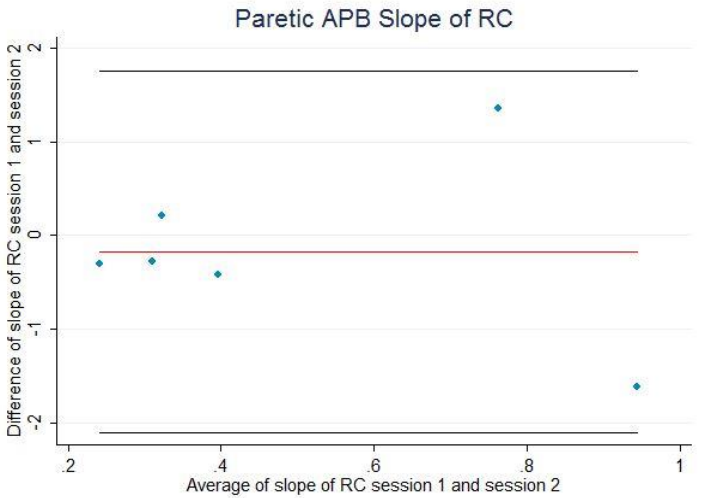


Figure 112B. Bland-Altman plot of the slope of the RC of the paretic APB, n=6

Figure 112A & B - Bland-Altman plots of the slope of the RC of the paretic ECR (A) and APB (B) assessed during slight muscle contraction. The x axis is the average slope of session 1 and session 2 plotted against (y axis) the difference in slope of session 1 and session 2, the red line is the mean difference line in the slope of session1 minus session 1. Plots A and B demonstrate random erroring agreement between sessions. Note the different scales of plots A and B. RC=recruitment curve, ECR=extensor carpi radilais muscle, APB=abductor pollicis brevis muscle.

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