Joel Restuccia

Effects of hypertrophy training on spinal & corticospinal excitability within the quadriceps muscle group.

Master's Thesis in Biomechanics

Autumn 2018

Faculty of Sport and Health Sciences

University of Jyvaskyla

Supervisor: Janne Avela

ABSTRACT

Restuccia, Joel, 2018. Effects of hypertrophy training on spinal & corticospinal excitability within the quadriceps. Department of Biology of Physical Activity, University of Jyvaskyla. Master's thesis in Biomechanics, 46pp.

The current study was designed to examine corticospinal modulation during a 10-week hypertrophy-training program including a 6-week detraining period. Furthermore, the study aimed to explain the origins or corticospinal adaptation. We compared motor evoked potentials (MEPS) over the time period in the vastus lateralis muscle by employing a range of transcranial magnetic stimulation (TMS) techniques including the input/output curve (I/O curve), short intracortical inhibition (SICI), intracortical facilitation (ICF) and the silent period (SP)

The main finding was that corticospinal excitability was reduced as the training protocol went on ($P = 0.005$) and then significantly rose after 3 weeks of detraining, followed by a reduction again after 6 weeks of detraining ($P = 0.016$). There were no significant differences found in short-intracortical inhibition (SICI), intracortical facilitation (ICF) and silent period (SP) ($P > 0.05$) or between bilateral and unilateral groups ($P > 0.05$) for all measurements.

The current results support the idea that initially when exposed to training, the corticospinal tract of a target muscle becomes less excitable but also introduces the effects that detraining may play in response to corticospinal excitability.

Keywords: Corticospinal excitability, TMS, Vastus Lateralis.

Abbreviations

CNS	Central Nervous System
CSA	Cross-Section Area
EMG	Electromyography
ICF	Intracortical facilitation
I-O Curve	Input-output curve
MEPS	Motor Evoked Potentials
MVC	Maximal Voluntary Contraction
RMS	Root Mean Square
rMT	Resting motor threshold
SICI	Short Intracortical Inhibition
SP	Silent Period
TMS	Transcranial Magnetic Stimulation

CONTENTS

1. INTRODUCTION

Resistance training can be dated back to ancient Greece as Hippocrates stated “that which is used develops, and that which is not used wastes away”. Until around the 1980s resistance training remained relatively unprofessional although with the likes of people such as Arnold Schwarzenegger gym numbers and types of machines to use significantly increased. There can be a range of reasons people partake in resistance training, this can include; increase physical aesthetics, physical health, rehabilitation, for sports performance and for the enjoyment of the activity. Training induces a range of adaptations to the body, the principle of specificity focuses on the idea that specific types of training elicits a specific response. More specifically adaptations made, as a result, hypertrophic training has been well documented.

Hypertrophy training is a technique of strength training with the goal to increase muscle growth as fast and/or as much possible. This differs from other programs that may have a focus on building strength gains or muscle endurance gains. This method of training was popularised from the year 2000 as Bryan Haycock discovered a training method that produced repeatable and predictable hypertrophic effects when resistance training. The ACSM recommends loads corresponding to 1-12 repetition max (RM) of the participant focusing on the 6-12 RM zone using 1-2 minute rest periods at moderate velocity using higher volume and multiple set programs for maximising muscle gain. Hypertrophy training has been shown to have an effect on the body’s neural, muscular, metabolic and hormonal function (Schoenfeld, 2010).

In the early stages of adaptations in response to hypertrophy training, the main changes in the nervous system can be observed resulting in an increase in strength. By the 6-7 week point muscle, hypertrophy becomes evident, which is when progressive overload becomes essential for muscle fibre recruitment and therefore further hypertrophy. More specific adaptations that take place due to hypertrophy training can include a change in neural function in previously untrained subjects. In the muscle; increase cross sectional area (CSA) and changes in muscle architecture, such as pennation angle, all leading to an overall increase in strength. (Schoenfeld, 2010)

The adaptations that take place within the neural function have been documented although there is some contradictory evident suggesting varied conclusions. It is important to assess these changes as there can be increases in strength without increases in muscle size. Changes

can be broken up into two categories, neural inhibition and neural facilitation. These can also be separated into spinal changes and supraspinal changes (changes with the origin at the brain). Previously adaptations in excitability have been represented with electromyography (EMG) and although results may vary depending on methods, EMG does not individually distinguish the place at which excitability changes take place.

When assessing spinal excitability changes within the muscles, the most common method selected is the Hoffman-reflex (H-reflex) although popularly used within the soleus it has been used in the quadriceps and a range of other muscles. Previously, it has been suggested that a stage of spinal period may reflect changes in spinal excitability.

It is also possible to measure supraspinal excitability through the use of transcranial magnetic stimulation (TMS). The first can include the use of motor evoked potentials (MEPS), with these data can be extracted from input/output curve (I-O curve), short-intercortical inhibition (SICI), intracortical facilitation (ICF) and the silent period (SP). SICI and ICF are paired pulse stimulations which result in either an inhibition or facilitation of the following MEPS depending on the time inbetween stimulations. The SP is a single pulse stimulation in which the break in EMG activity following the MEPS can be recorded.

The current study therefore is an attempt to draw conclusions on the best methods and current knowledge involved in spinal and supraspinal excitability involved in hypertrophic training.

2. NEUROMUSCULAR SYSTEM

2.1 Central Nervous System

Human motor control is made possible from a series of connected anatomical regions. This includes the primary motor cortex, premotor cortex, supplementary motor cortex, basal ganglia, thalamus, cerebellum, brain stem, midbrain, reticular formation and the spinal cord (Kandel et al. 2000, 8-10). Simply put, the nervous systems generates the signals allowing the muscles to produce force (Rainoldi & Gazzoni, 2011). Muscles are made up of many fibres and to ensure the fibres contract they are divided into motor units. Motor units comprise of a motoneuron and the fibres that it signals (Figure 1). These are found within the muscle cross section and are fused with fibres that are connected to other motor units. This means that a muscle may consist of a range of physiological functions. (Cardinale et al. 2011, 17-18)

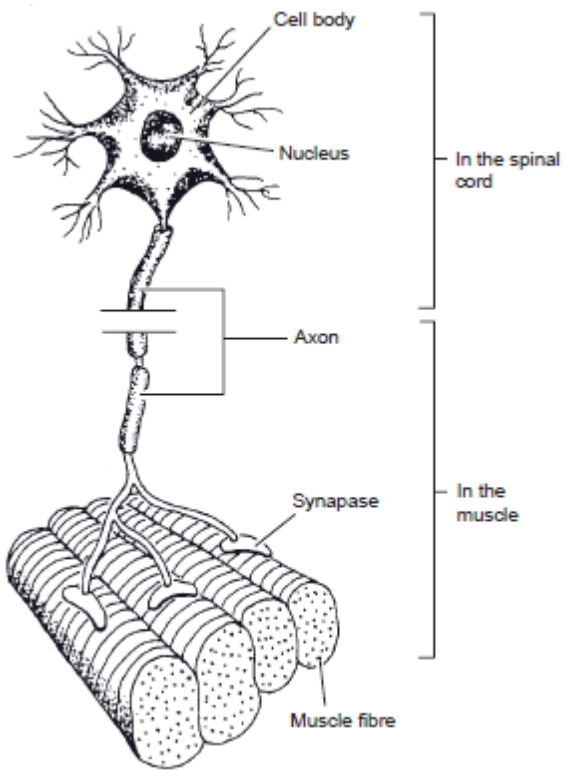


FIGURE 1. A motor unit, revealing the connection between the spinal cord and the muscle. The motor nerve branches out to connect with many muscles through synapses. Source: Cardinale et al., (2011)

Muscular conduction velocity is the rate at which action potentials move along the fibre, this rate is highly dependent on the diameter of the axon, the smaller the diameter the smaller the conduction velocity (Rainoldi & Gazzoni, 2011). The mechanisms that control the nervous and muscular transmissions is the depolarization induced by sodium and potassium as well as the conduction from one node of Ranvier to the next resulting in two different average conduction velocities which is essential to complete two different tasks. The first is to provide information to the central nervous system (CNS) to allow for the correct reaction and the second is to allow the timely contraction of muscle fibres. This is significant as when the muscle cross section area hypertrophies, a maximal voluntary contraction (MVC) can be increased in spite of little or no change to the fibre type within the muscle. (Rainoldi & Gazzoni, 2011)

2.2 Muscle Physiology

Skeletal muscles are contracting cells that is supported by connecting tissue. The muscle is organised in a hierarchical fashion which in order includes fascia, epimysium, endomysium, sarcolemma in which contains the basal lamina (Figure 2, left). The layers connect together forming tendons at the end of the muscle. Futhermore, a muscle fibre or myofibre are made up of smaller units known as myofibrils, these are contractile stuctures made up of actin and myosin which are organised in a sarcomere (Figure 2, Right) which is responsible for muscle contraction. (Cardinale et al. 2011, 3-4)

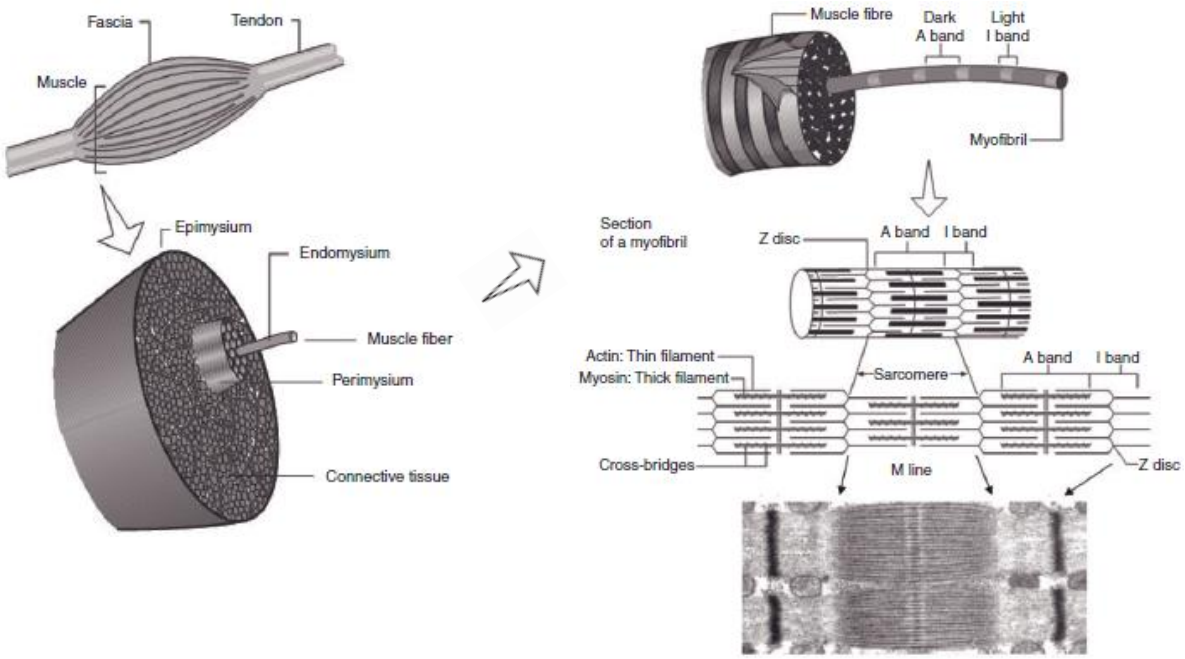


FIGURE 2. Skeletal muscle hierarchical macrostructure (left) and mircrostruture (right). Source: Challis (2000)

2.3 Force production

Force produced from a muscle is reliant on a range of factors which include, the mechanical properties of a muscle, the muscle architecture and the rate and number of motor neurons that have been activated. The mechanical properties of a muscle rely on two major factors which can include force–length relationship and force-velocity relationship which in turn is influenced by the organisation of the muscle. The force-length relationship is dictated by the cross bridge theory or muscle contraction. The force produced by a muscle is reliant on the length of which that muscle is at, as the length increases so does the number of available actin binding sites up to an optimal point then reduces (Figure 3). The force-velocity relationship displays the decrease in force with an increase of speed as the muscle shortens and an increase of force with an increase muscle-lengthening velocity (Figure 4). (Enoka, 2008, 228-230)

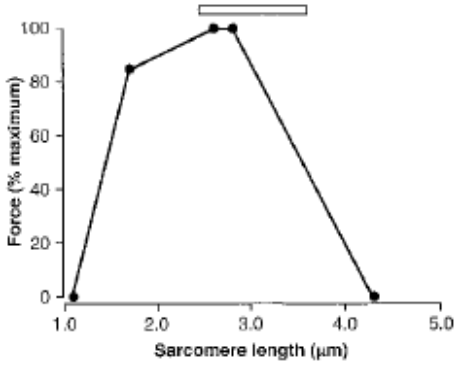


FIGURE 3. Force length relationship revealing that force production is heavily dependent on muscle length as seen when the muscle is longer or shorter than optimum. Source: Enoka, 2008

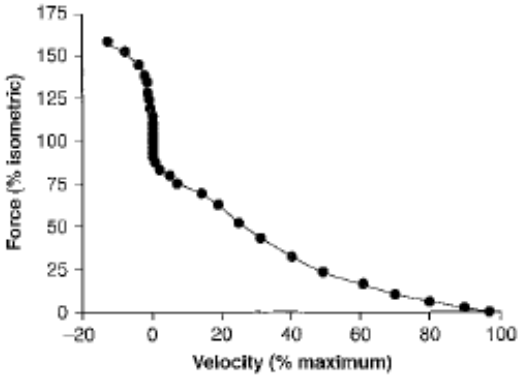


FIGURE 4. Force velocity relationship revealing the decrease in force as the velocity increases. Source: Enoka. 2008

2.4 Motor Unit recruitment

In order to produce a movement, it has been shown that motor units recruit in an orderly fashion, which is to say that there is a fixed sequence. To produce a larger amount of force, more motor units within the muscle must activate and to reduce force motor units will deactivate in a way that the last unit activated will become the first units to deactivate. Henneman et al., (1974), have revealed this through the size principle. The size principle dictates that motor units will be activated in order from slowest to fastest until maximum voluntary contraction. Reducing force is completed by the opposite, reducing the firing rates of the largest to the smallest. This is essential in human muscle modulation.

2.5 Muscle Fibre types

Skeletal muscle is made up of a range of fibre types that differ in, molecular, metabolic, contractile and structural characteristics, although a key component of the fibres is their ability to adapt. Type 1 muscles fibres are known as slow as a result of their slow isoform contractile proteins as well as high volumes of mitochondria, myoglobin, oxidative enzyme capacity and capillary density. Type IIA also known as fast due to the fast contracting fibres that contain a moderate resistance to fatigue as well as a high oxidative capacity. Type IIB fibres contain high glycolytic activity a low resistance to fatigue and a low mitochondrial density. (Cardinale et al., 2011, 9-10)

2.6 Muscle architecture

Muscle architecture has functional significance and is the arrangement of myofibres in the muscle, comparative to the axis of force generation. There are many different types of arrangements but they can mostly be either described as fusiform or pennate. Fusiform fibres are arranged so that the fibres are parallel to the force generating axis and has a longitudinal architecture while pennate fibres have an oblique angle to its force generating axis. As well as these, other important factors involved in generating force is muscle and fibre length. The velocity of a muscle is seen as proportional to its fibre length. Shorter muscles with similar cross sectional areas (CSA) are best applied to activities with force production with a low velocity, for example the soleus mainly acting as an antigravity postural muscle. Whereas the biceps femoris has a similar CSA but is much longer and therefore it is more suitable for generating high velocity. (Cardinale et al., 2011, 10-11)

3. NEUROMUSCULAR ADAPTATION

3.1 Muscle Fatigue

Fatigue is the visible impairment of an output reduction for example, force, torque or a specific motor task. There are three different sites which can induce fatigue and are known as central, peripheral and fatigue of the neuromuscular junction. Central fatigue, which is known as fatigue of the primary motor cortex and the central drive to motor neurons, can be revealed through a reduced MVC because of reduced firing rates. This is shown through the use of an artificial stimulation to the motor cortex whilst a participant is performing an MVC. When applied, if the stimulation produces an increased force output it can be said that the participant is showing central fatigue. Peripheral fatigue is known as the fatigue associated with the changes at or distal to the neuromuscular junction (Gandevia, 2001). It is possible to study peripheral fatigue by observing a change in tetanic force (MVC + superimposed twitch) as well as a change in passive twitch force (Kent-Braun, 1999). Lastly, fatigue can also impair neuromuscular propagation that is a reduction in force output due to either a failure in axonal action potential, excitation-secretion coupling, and a rediction in neurotransmitters or a decrease in post synaptic receptor sensitivity. (Spira, Yarom and Parnas, 1976)

3.2 Training adaptation of the neuromuscular system.

As previously mentioned, there has been evidence of an increase in strength gains without a significant change in muscle characteristics, which leads to the idea of a contribution from neural factors (Aagaard et al., 2002). To further understand this it is important to look at the features on a more detailed level, due to the fact that the intensity of the neural drive may or may not increase in strength or power training (Duchateau & Baudry, 2010). The majority of the evidence concerned with neural adaptations in response to strength training is indirect and therefore happen at either one or both of supraspinal or spinal levels. The supraspinal level concerns corticospinal neurons, subcortical neurons, as well as inhibitory and excitatory intercortical neurons while the spinal level pertains to motor neurons and inhibitory and excitatory neurons. (Aagaard et al., 2002)

3.3 Hypertrophy training

Hypertrophy is the increase in muscle fibre size or mass as a result of an accumulation of contractile and non-contractile proteins within the cell (Cardinale et al., 2010, 11-12). Hypertrophy training has an impact on all muscle fibre types although type II fast fibres have

been the most sensitive to training. (Aagaard et al., 2001). Interestingly, satellite cells, which have a significant contribution to muscle hypertrophy, are equally distributed between type I and type II fibres. High tension applied over the skeletal muscles throughout strength training encourages the hormone IGF - 1. Briefly, IGF - 1 activates protein kinase B signalling pathway which regulates protein synthesis. Mechano-transduction may also stimulate muscle growth through muscle tension (Schoenfeld, 2010). Aagaard et al., (2001) noted that muscle architecture can be altered with hypertrophy training, for example hypertrophy of the calf muscle can increase pennation angle. This may even come to a point in which reduces speed production or force. (Duchateau & Baudry, 2010)

Muscle hypertrophy arises from protein synthesis exceeding protein breakdown. Satellite cells usually remain dormant and serve as reserve cells although when sufficient mechanical stress is placed on the muscle they proliferate and create new myofibres allowing for the growth of new muscle tissue. They have the ability to fuse with existing myofibres that are critical for the increase of muscle cross sectional area. Satellite cells also contain regulatory factors that help in muscle repair, regeneration and growth; they have the ability to bind to sequence specific DNA within the muscle gene promotor. (Cardinale et al., 2010, 11-12)

The three main factors associated with commencing the hypertrophic response include mechanical tension, muscle damage and metabolic stress. (Jones & Rutherford, 1987) A significant factor for muscle growth is tension produced by force generation and the stretching of a muscle and it is thought to be controlled by altering the integrity of skeletal muscle causing molecular and cellular responses in satellite cells and myofibres (Fry, 2004). This can be clearly seen during eccentric contractions and has been employed as a technique used for hypertrophy training as hypertrophy occurs from the lengthening of elements such as collagen and titin augmenting the active tension (Schoenfeld, 2010). Although tension alone has been found to result in muscle hypertrophy, it has also shown to induce neural adaptations without muscle hypertrophy (Cote et al., 1988), suggesting the need for more elements to result in hypertrophy. Training the results in muscle damage such as the deformation of membranes, T tubules and tearing of membranes has been linked to the response myotrauma. Damaged fibres attracts macrophages, myoblasts and lymphocyts which then leads to satellite cell proliferation which mediates muscle growth. (Toigo & Boutellier, 2006) Metabolic stress is a result of exercising at a rate that uses ATP production or, anaerobic glycolysis resulting in the build-up of lactate, inorganic phosphate and creatine (Schoenfeld, (2010), Buresh et al., (2009)) hypothesised that

the acidic environment led to fibre degradation and a stimulation of sympathetic nerve activity leading to a hypertrophic response.

4. NEUROMUSCULAR MEASUREMENT TECHNIQUES

4.1 Surface EMG for neural activation

When an end-plate potential is generated, usually a muscle fibre action potential transmits to the end of the muscle fibre. The current that is generated can then be recorded with electrodes; the recordings are called electromyograms (EMG). EMG can be used to diagnose issues in the neuromuscular junction, to determine the requirements of job related tasks, identify mechanisms involved with the neuromuscular system and also to asses muscle force. (Enoka, 2008) Recording EMG reveals the peripheral and central properties of the neuromuscular system, which is based on the dependence of the membrane properties or the muscle fibres and the timing of the muscle unit action potentials. Electrodes can range from sizes and materials, when in the process of recording muscle the electrodes are placed on the skin over the belly of the target muscle. (Farina et al., 2010)

EMG records the timing and intensity of the muscle activation by the nervous system although it is very important to note that EMG amplitude can be very sensitive to measurement technique (Enoka, 2008), there are many factors that influence the surface EMG which include nonphysiological and physiological factors that can be seen in Figure 5.

Although there have been problems associated with EMG some approaches have been employed to minimise the effects of these problems. EMG recordings may underestimate the output from the spinal cord it is possible to express EMG amplitude relative to the MVC recording which reduced the limitation of amplitude cancellation. Electrode placement is also essential and recommendations for the placement of various muscles can be found to combat this limitation. Next, filtering can be applied which modifies frequencies to help eliminate possible interference from noise. Crosstalk is also a modifiable factor that occurs when a signal is produced by a muscle is not the one targeted by the electrodes. To combat this it can be useful to compare a differential recording with a double differential recording, without cross talk the single and double differential signals will have similar amplitudes. (Enoka, 2008, 197-200)

Category	Factors
	NONPHYSIOLOGICAL FACTORS
Anatomical	Shape of the neuromuscular system
	Thickness of the subcutaneous tissue
	Size and distribution of motor unit territories
	Number and distribution of muscle fibers innervated by each motor neuron
	Muscle fiber length
	Spread of the end plates and tendon junction within and among motor units
	Range of pennation angles
Measurement system	Electrode size, shape, and placement
	Skin-electrode contact (impedance, noise)
Geometrical	Muscle fiber shortening
	Movement of the muscle relative to the electrodes
Physical	Conductivity of the tissues
	Cross-talk from nearby muscles
	PHYSIOLOGICAL PROPERTIES
Fiber membrane	Average conduction velocity
	Distribution of conduction velocities
	Shape of intracellular action potentials
Motor unit	Number of activated motor units
	Distribution of discharge rates
	Synchronization

FIGURE 5. Enoka's adaptation of Farina et al., (2004) of nonphysical and physical factors influencing the recordings of Surface EMG. Source: Enoka (2008)

Before analysing the data, the signal goes through a process of rectification in which the value of the EMG signal is rectified and then smoothed which is then averaged over an interval of time. Root mean square (RMS) can as be calculated and reflects the average power of the signal which correlates amplitude variates during a contraction. (Farina et al., 2004)

4.2 Transcranial magnetic stimulation (TMS)

TMS is a non-invasive neuro stimulation technique to study brain behaviour and cortical excitability based on electromagnetic stimulation of an electric field in the brain. It can be utilised in order to assess the response of cortical and corticospinal pathways (Avela & Gruber, 2010, 118-119) and how they may change throughout an intervention. In 1985 Barker et al. first used this technique by demonstrating the possibility to activate the corticospinal pathway using a magnetic field. Due to its safety and convenience, TMS has become a popular device to study human motor control, evaluate corticospinal transmission and perform functional mapping (Avela & Gruber, 2010, 118-119). To produce a magnetic stimulation, a rapidly changing current pulse is created from a magnetic coil which is placed over the motor cortex which then leads to an electrical current penetrating the brain and depolarising the membrane,

in turn producing an excitatory or inhibitory postsynaptic potential (Hallet, 2000). The initial magnetic stimulator coils were circular; these are thought to activate neurons that lie 1.5-2.0 cm below the scalp surface. Using this coil becomes most problematic due to the relative uncertainty of the site of stimulation (Pascual-Leone et al., 2002). As a result of this issue, the figure 8 coil was invented which comprised of two circular coils placed together side by side so that the currents are flowing in opposite directions making it significantly more popular due to the selectivity stimulation of a 5mm resolution (Figure 6). The greatest advantages of using this coil is the ability to also stimulate the muscles in the legs and well as subject comfortability due to the focal stimulation. Furthermore, the coil has been developed into a double cone coil in which the figure eight coil is connected at an angle of 90-100 degrees for deeper brain penetration (Avela & Gruber, 2010, 118-119).

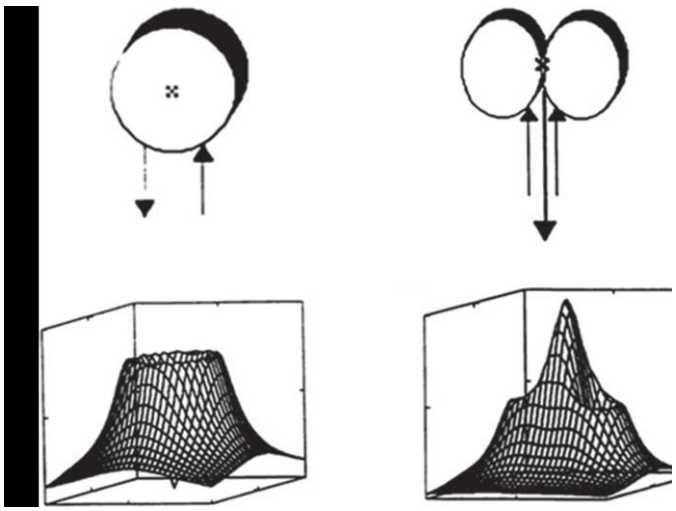


FIGURE 6. A diagram depecting the focal ability of the newer figure 8 coil when compared with the original circular coil. The figure 8 coil has the ability to more specifically stimulate the desired site. Source: Hallet, (2007)

4.3 Motor evoked Potential (MEP).

To produce a short latency response, TMS must excite pyramidal neurons at or before the cell some, not directly at the axons of corticospinal cells. As a result of the following combination of volleys coming from a range of pathways motor evoked potentials (MEPs) are recorded with surface electromyography (EMG) on the target muscle. When using TMS in comparison with transcranial electrical stimulation (TES) it is generally accepted that volleys created by TMS are indirect waves (I-waves) although there is a possibility to elicit at high intensities direct

waves (D-waves), which is applicable as a shift in MEP latency during measurements suggests a change of site stimulation. This is due to the indirect activation of the pyramidal cells. Furthermore, the activation site is made up of axon collaterals of pyramidal cells, intracortical interneurons and a range of other associated fibres from other cortical areas. Arai et al., 2005 suggests facilitatory interneurons are aligned in one direction while inhibitory neurons align in a range of direction, meaning that the direction of the current with TMS has a significant effect on the MEP created.

Motor Evoked potential with muscle activity

Muscle activity has a significant effect on MEPs, although it has been shown that this effect can range depending on the muscle. However, it can be said that it increases the size of the MEP at the same stimulation levels as well as reducing the motor threshold (MT) in the muscle. Di Lazzaro et al., (1998) stated that voluntary contraction increases MEP size, as there is an increased excitability of motor neurons and motor cortical output cells.

4.4 Input-output Curve.

The Input-Output Curve (IO Curve) is a basic stimulation-response technique, which results in a MEP plotted against stimulation intensity curve (Gangitano et al, 2002) or otherwise known as the MEP recruitment curve. It is important to first define the resting motor threshold (rMT) when the target muscle is in a passive condition. Overall, the rMT represents the corticospinal pathway excitability in general terms which means that it covers the large pyramidal cells, cortical excitatory and inhibitory neurons as well as the spinal motor neurons (Avela & Greuber 2010, 118-120). The rMT has both been defined as the smallest TMS intensity that produces a repeatable MEP of at least 50μ in either 5 out of 10 consecutive trials or 3 out of 5 consecutive trials. Devanne et al. (1997) first implemented it, when they showed that the relationship between the intensity of the stimulus and the output size of the MEP is nonlinear but rather has a shape following a sigmoidal curve. The expected shape of an I/O curve can be seen in Figure 7. Although in many cases which usually involve those muscles of the leg where rMT is much higher than in the hand, the plateau phase of the sigmoidal curve may not be reached (Avela & Gruber, 2010, 120-122).

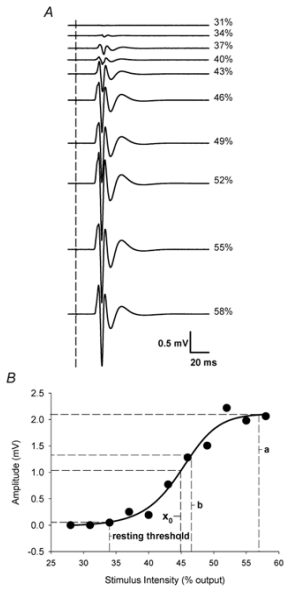


FIGURE 7. A representation of the I-O Curve, the relationship of the increased stimulus intensity to the increased MEP revealed in a sigmoidal pattern. Source: Pitcher et al., (2004)

4.5 Short-Intracortical Inhibition & Intracortical Facilitation

An important function of TMS is its ability to not only evaluate corticospinal ability as previously mentioned using a single pulse stimulation technique. It has also been shown that it is possible to employ a paired pulse stimulus technique, the second pulse produced directly after the initial pulse will create and inhibition or facilitation which is dependent on the time delay between the stimulus' or also known as the interstimulus interval (ISI). It has been shown that using the paired pulse stimulus, an initial pulse (conditioning stimulus) was able to influence the second pulse (test stimulus) as a result of the ISI. When the ISI has been 1-6ms short intracortical inhibition (SICI) has been shown, although when there has been as ISI of 10-15ms Intracortical facilitation (ICF) was revealed (Figure 8). (Avela & Gruber, 2010, 120)

Reynolds & Ashby, (1999) suggested that the intracortical inhibitory mechanisms play a functional role at the start of the initial contraction, this notion is supported by Floeter and Rothwell, (1999) who claimed the mechanism of SICI can be described as "releasing the brakes before pressing the gas pedal". This proposes this idea that inhibition may indirectly have an influence on movement production and that the response can be altered with training.

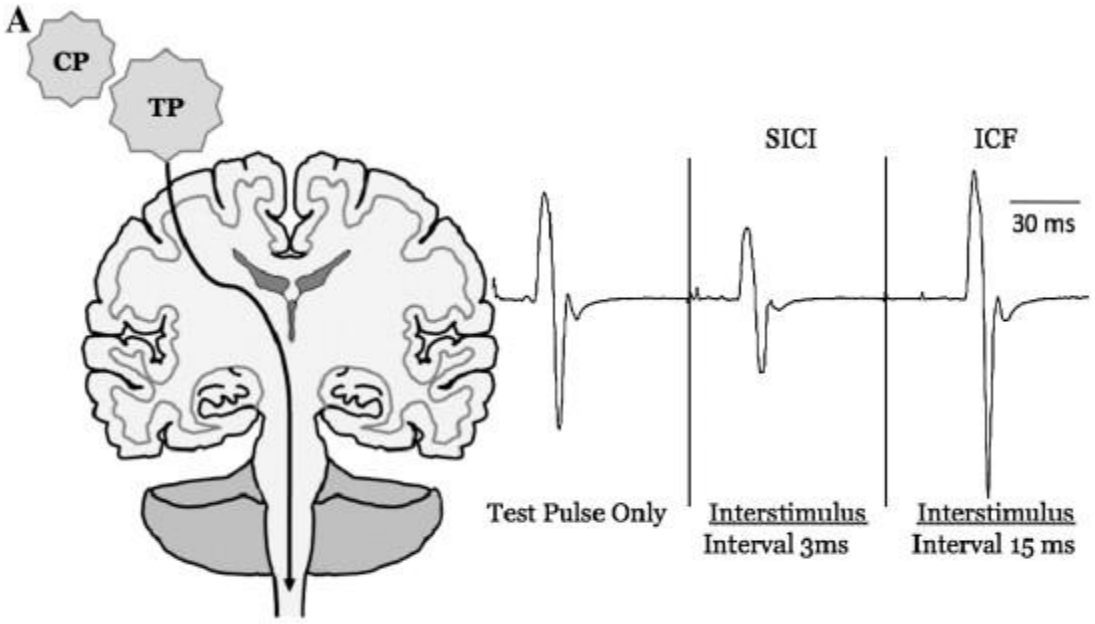


FIGURE 8. SICI & ICF, revealing the effect on the ISI on the test protocol. Source: McGinley et al. (2010)

4.6 Silent Period

When a single pulse stimulus is applied during a contraction, there is a break in EMG activity after the MEP. This break is known as the Silent Period (SP) (Figure 9). It has also been shown that generally when the TMS stimulus increases, as does the duration of the SP. The exact mechanism of the SP is unknown although it is generally accepted to have both spinal and cortical origins. Chen et al., (1999) and Ziemann et al., (1993) propose that the depression of the reflex during the early stage of SP is as a result of the spinal mechanisms although after the H-reflex has recovered, the concluding part is thought to of been form a cortical origin.

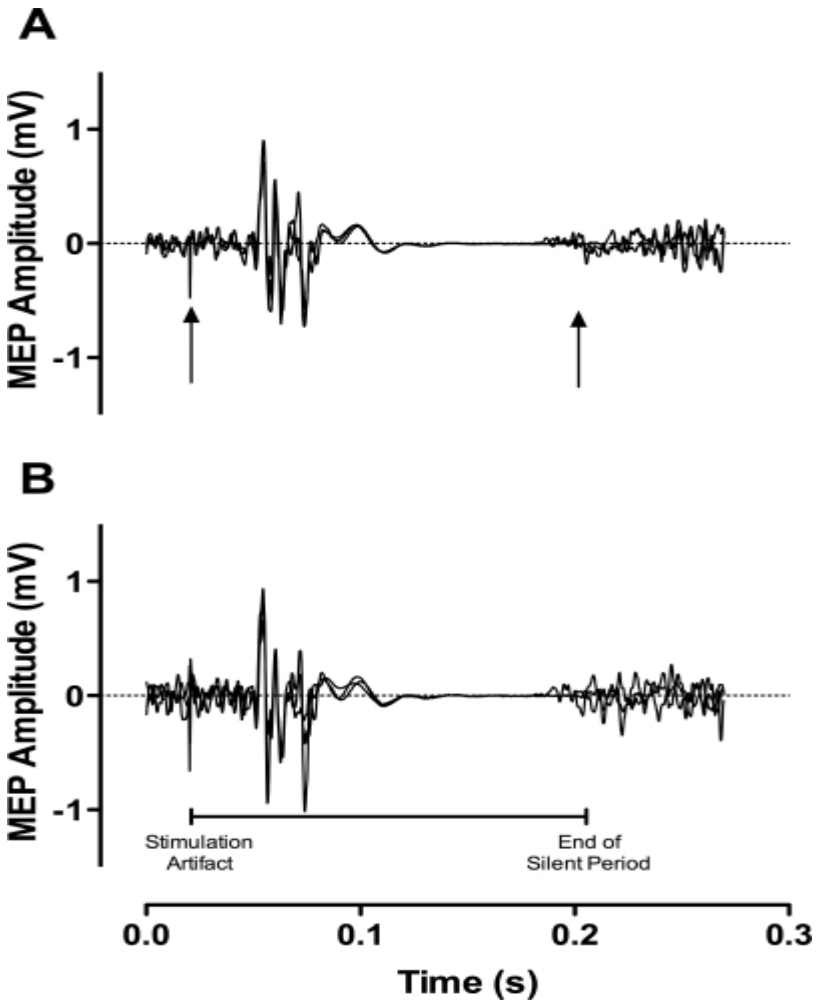


FIGURE 9. Cortical Silent Period. Source: Tallent et al. (2012)

5. THE PURPOSE OF THE STUDY

Previously literature has examined the effects of a 60 day unilateral strength training program with 40 days of detraining, after each 20 days MVC, EMG and CSA was taken in the vastus meadialis, lateralis and rectus femoris. It was concluded that hypertrophy accounted 40% of the increase in force while 60% can be attained as a result of increase in neural drive and muscle architecture (Narici et al., 1989). Furthermore Aagaard et al., (2000), conducted a 14 week progressive heavy resistance training protocol investigating electromyography activity in the quadriceps. It was demonstrated that EMG activity increased for all the quadriceps muscles and the results were recorded highest during a concentric contraction in untrained subjects. These studies conclude that as a result in changes in EMG, adaptations in neural drive can be attained from resistance training.

On the other hand Cannon & Cafarelli (1987), observed adaptations in response to progressive resistance overload training 2 days per week for 5 weeks. Although there was a significant change to MVC, no significant difference was found in the neural drive through EMG. The authors suggest that there may be some central motor adaptation but it is not revealed through EMG. Additionally, Thorstensson et al. (1976), studied the effects of an 8 week progressive strength training program on the leg extensor muscles. They found that post training there was a slight decline in EMG with only minor findings in changes of muscle fibre size and composition.

Although results differ, there are often issues associated with the methodological limitations when recording surface EMG. There was also disparities regarding the amount of training conducted in each experiment with different exercises, which would lead to varying adaptations.

In order to gain a greater understand in the area of excitability Aagaard et al. (2002), produced an experiment in which participants took part in a 14 week heavy resistance training program to observe V-wave and H-reflex responses examining neural adaptation within the soleus muscle. Shortly, the H-reflex is a reflex recorded through EMG by performing a submaximal electrical stimulation to a peripheral nerve. Furthermore a maximal stimulation induces a compound action potential known as a M-wave, this eradicates the H-reflex in a resting condition. Moreover the V-wave is the voluntary correspondent of the H-reflex, for the EMG to be observed the voluntary drive must be greater than the M-wave abolishment. Increases in

evoked V-wave and H-reflex responses were observed during MVC, suggesting the possible evidence that there was an enhanced neural drive in descending corticospinal pathways and motorneuron and α-motorneuron excitability revealing the possible plasticity for spinal mechanisms. (Aagaard et al., 2002) This experiment paved the way for the use of more advanced techniques in the exploration of spinal and supraspinal excitability.

The purpose of the current study was to assess the response of the cortical and corticospinal pathways involved in a hypertrophy-training program as well as looking at the response to detraining. The study was designed in a way in which it furthermore examines the effect that unilateral or bilateral traning may have on the results. This idea rose through the disparity in previously results leading to the question of neural input when exploring strength gains. To the knowledge of the author, no previous studies have looked at the effects of the brain throughout the detraining period in a similar fashion.

The main hypothesis is that the subjects will improve sensitivity from the pathway of the brain to the leg after the hypertrophy-training program.

6. METHODS

Subjects. Twenty six healthy male subjects were broken in to 2 groups of 13 people, unilateral (age 24.9 ± 4.1 S.D, height (cm) 179 ± 4.6 and weight (kg) 75.2 ± 9.8) and bilateral (age 24.2 ± 4.5 S.D, height (cm) 182 ± 9.2 and weight (kg) 78.8 ± 10.2) respectively with no history of previous strength training or injury within the last three months participated in the study. Each subject gave their written informed consent after an explanation of the experiment and the associated risks that may be involved. All subjects were volunteers and received no monetary compensation for their involvement. The methods were approved by the local university ethics committee of the University of Jyväskylä and performed according to the Declaration of Helsinki.

Experimental design. The study consisted of seven testing sessions before during and after the hypertrophy training protocol during weeks -1, 0, 2, 5, 10, 13, 16 with week's 1-10 consisting of the hypertrophy training program and 11-16 observing the effects of detraining. During the initial testing week participants were subjected to experiencing ultrasound, isometric tests, TMS, EMG and isokinetic dynamometer procedures. Each week the testing protocol remained that same. EMG data was recorded from the VL. Each session began with a warm of up MVC's followed by and MVC then a range of TMS procedures.

Hypertrophy training Protocol

Training included progressive heavy resistance hypertrophic type of training. The primary muscle groups of interest were knee extensors and elbow extensors. Knee flexors and elbow flexors are trained, but not tested. Training included 80-85% of dynamic and 15-20% of isometric training. Subjects trained three times per week (Tuesday/Wednesday, Friday, Sunday). On friday subjects started from legs and then moved on to the upper body. On Sunday it was vice versa to minimize the order effect. The focus was increasing strength and muscle mass. Subjects begin the intervention with three easy weeks, followed by four hard weeks and finally three medium weeks. The volume of training increased over the first seven weeks, then the volume decreased and the training intensity increased. Training volume was equal for both groups. During the intervention subjects will have protein/CHO supplement after every workout. For a detailed program see appendicies.

Experimental Protocols. During the protocol the participant was sat on the isokinetic dynamometer (Neuromuscular Research Center, University of Jyväskylä), the chair and head were adjusted for the participants comfort and the knee angle was set at 90 degrees (Figure 10). For the warm up the participants completed two contractions at 50% and 80% of the MVC followed by two attempts to record MVC. After, the participant was asked to relax and the corresponding part of the motor cortex to the right VL was found utilizing TMS. 10 different stimulations at 100, 110, 120, 130 and 140% of RMT were utilised in order to obtain results for the I/O curve. AMT was then found at 10% of MVC and 10 stimulations were produced for SICI and ICF at 80% and 120% of AMT, following this 5 stimulations were used to determine the silent period using 120% of AMT and 50% of MVC.

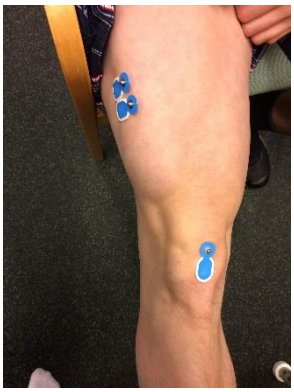


FIGURE 10. EMG placement, electrodes were placed on the VL of the right leg and a 'ground' electrode placed on the patella.

Electromyography. EMG activity was recorded for the VL of the right leg using self-adhesive electrodes (Blue Sensor N, Ag/AgCL, 0.28cm²), in a bipolar setting with a ground electrode was placed on the patellar (Figure 10). Electrode placement and skin preparation was performed according to SENIAM recommendation for the VL muscle. In order to ensure consistency in the placement of the electrodes a small tattoo was placed on the participants, this was 2/3 on the line from the anterior spina illiaca superior to the lateral side of the patellar. EMG signals were amplified and high pass filtered (x1000, 10Hz) by a preamplifier (NL824, Digitimer Ltd., Herfordshire, UK) then bandpass filtered (10Hz to 1KHz) by a different amplifier (NL900D/NL820A Digitimer Ltd., Hertfordshire, UK). The signals were acquired via a 16-bit AD converter (CED power 1401, Cambridge Electronics Design Limited, Camridge, UK).

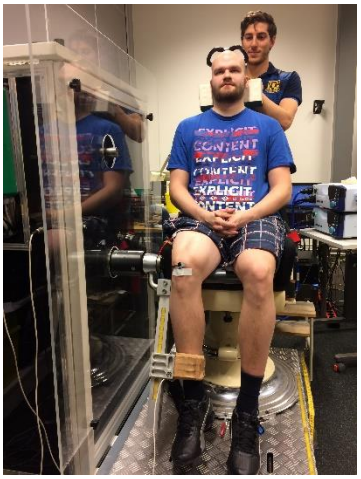


FIGURE 11. Experimental Set-Up

Transcranial magnetic stimulation. TMS was delivered using double pulse, Magstim Bistim² Stimulator with a 7-cm figure-eight shaped TMS coil (Magstim, Whitland, UK), in which directs the current posterior-anterior towards the motor cortex. The coil was positioned on the participant in the place that elicited the greatest MEP amplitude at rest, furthermore subjects scalps were marked in order to keep the coil position constant and ensure corrected re positioning. Moreover stimulations were randomised to reduce subject anticipation. RMT was defined as the lowest stimulus intensity to elicit a visible MEP with a peak-to-peak amplitude of 50μV in three out of five consecutive trials. AMT was defined as the lowest stimulus intensity to elicit and visible MEP with a peak-to-peak amplitude of 200μV in three out of five consecutive trials (Rossini et al., 1994) with a contraction of 10% of MVC. I/O Curve was found with 10 stimulations at 100, 110, 120, 130 and 140% of RMT while SICI and ICF was foundwith 10 stimulations at 80% and 120% of AMT with an interstitial stimulus interval of 3 and 15ms respectively. Finally Silent Period was found with 5 stimulations of 120% AMT at 50% of MVC.

Statistical analysis

Data analysis was performed off-line using Spike2 v4. Software (CED, Cambridge, UK). This program was utilized in order to synchronize stimulation, dynanmometer force outputs and EMG. Peak-to-peak and MEP Area was calculated as the average of 10 trials per variable (100%, 110%....140%) for I/O curve, SICI and ICF after normalising data. MEP Area data was altered using the 'Smooth' function within Spike in order to compensate for noise seen during

some trials. Input/Output MEP Amplitude graph was gained from averaging each intensity (100-140%) obtained from the entire week. The Silent Period was measured from the onset of the stimulation to the return of the EMG activity seen visually by the examiner. The results have been presented as means with standard deviation (SD). TMS trials were averaged for each set of stimulations. T-test were used when comparing effects of different time points as well as two way repeated measures ANOVA when comping differences between unilateral and bilateral conditions. Data is presented as means with standard deviation.

7. RESULTS

The results have been represented as the weeks of measurements during the protocol, the initial weeks are 0, 2, 5, 10 which represent the week of the training program, following this there is d3 and d6 which represent the detraining periods of three weeks and six weeks. Data is referred to as Pre (0) Post (10) and retention (d6).

Force

As seen in Figure 12 isometric knee extension significantly increases from pre (0) to post (10) (p=0.001) as well as from post (10) to three weeks of detraining (d3) (p=0.001)

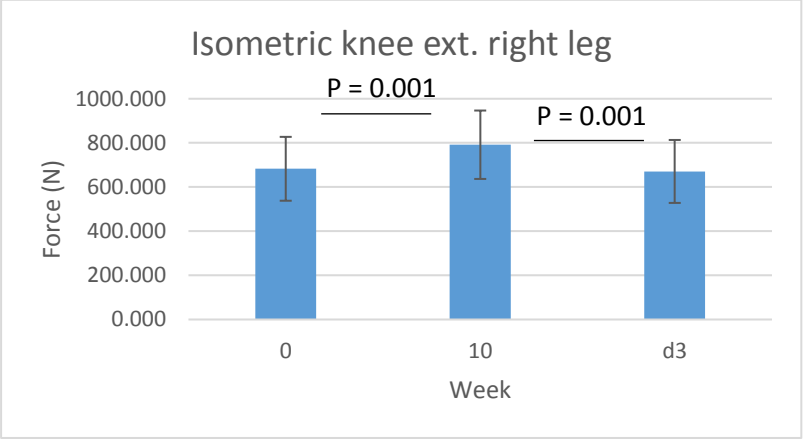


FIGURE 12. Force output isometric knee extension (right leg), Data presented as mean ± 95% CI.

Cross Sectional Area

As seen in Figure 13, there is a significant change is cross section area between pre (0) and post (ST 10wk) (p=0.046) and although not significant there can be observed changes within ST 10wk and DT 6wk.

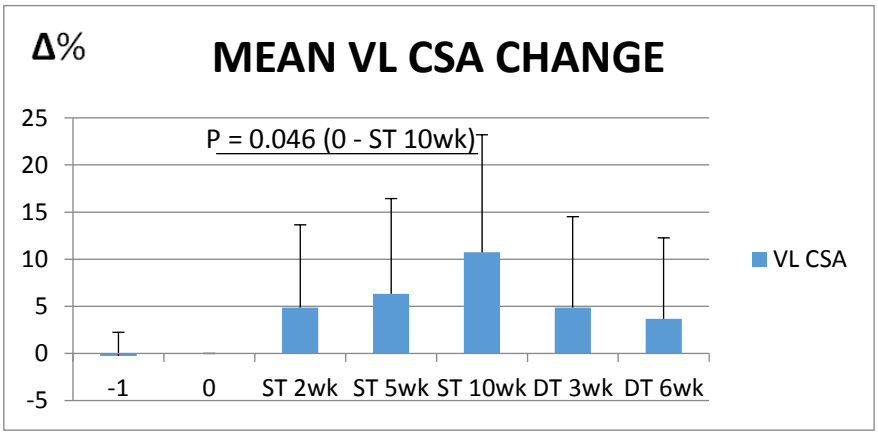
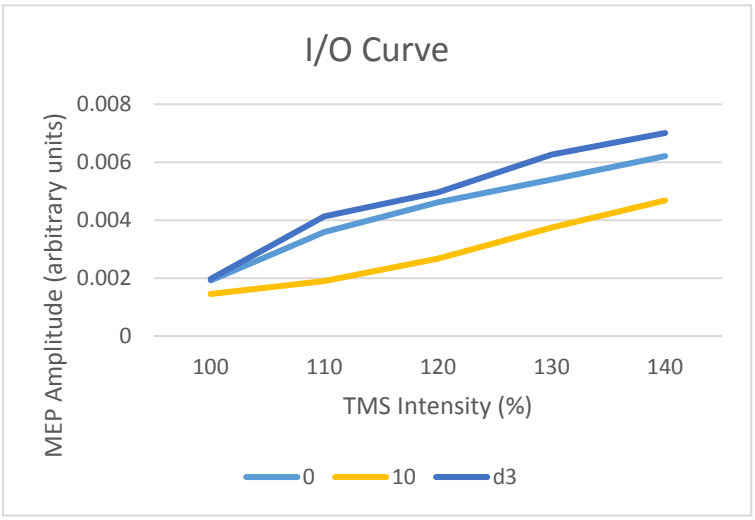
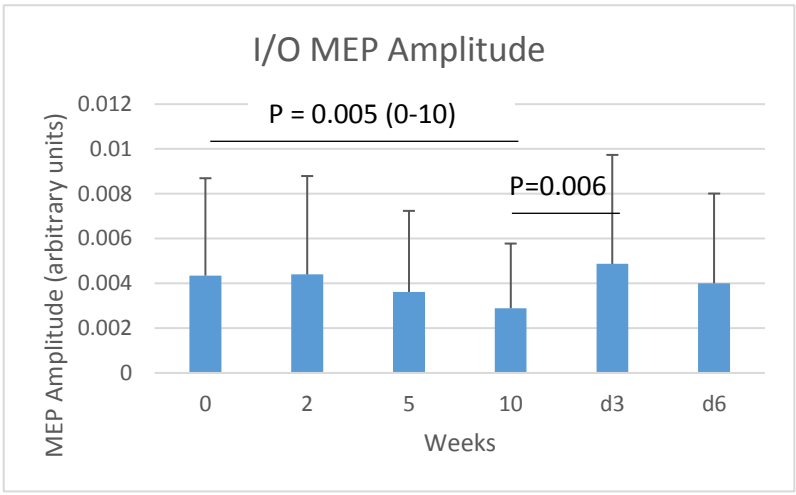


FIGURE 13. Cross Sectional Area changes when compared with week 0 (%). Data presented as mean ± 95% CI.

TMS

As shown in Figure 14a and 14b, the T-test of normalised MEP amlitude depicted a significant difference between the pre (week 0) and post (week 10) measurements (P = 0.005) and post (week 10) and 3 weeks after detraining (week d3) (P = 0.006). Hypertrophy training had no significant effect on ICF (Figure 16) (P = 0.183) pre to post measurements and (P = 0.511) post to detraining measurements. Reguarding SICI (Figure 15), no difference in value was found between Pre and Post measurements (P = 0.369) as well as post to retention (P = 0.927). The SP (Figure 16) also exposed no significant differences between pre and post (P = 0.289) and post and rentention (P = 0.681).





FIGURES 14a & 14b. Effect of hypertrophy training protocol on the I-O Curve (a) and I/O MEP Amplitude (b). Data presented as mean ± 95% CI.

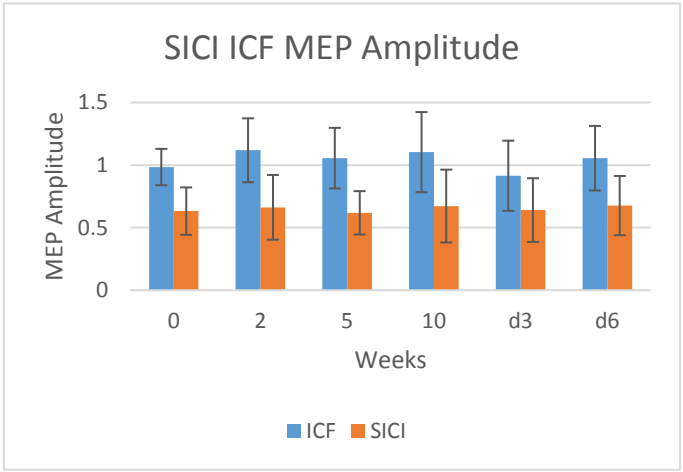


FIGURE 15. Effect of hypertrophy training protocol on SICI and ICF. Data presented as mean ± 95% CI.

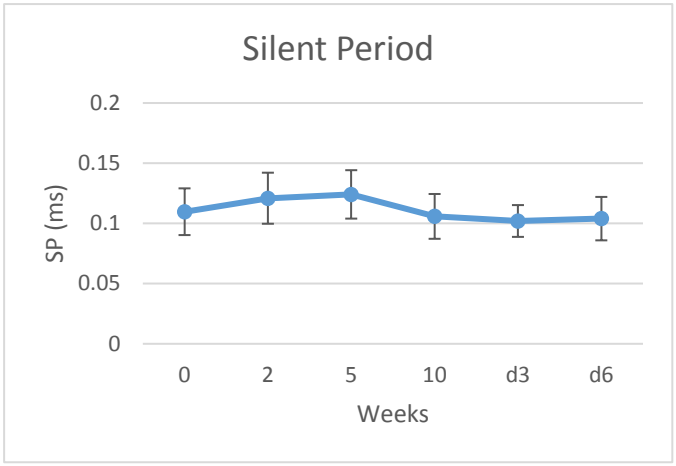


FIGURE 16. Effect of hypertrophy training protocol on the Silent Period. Data presented as mean ± 95% CI.

Unilateral vs Bilateral

Changes in VL were not statistically significant for either group although the graph reveals similar trends to that of the particiapants combined. (Figure 17)

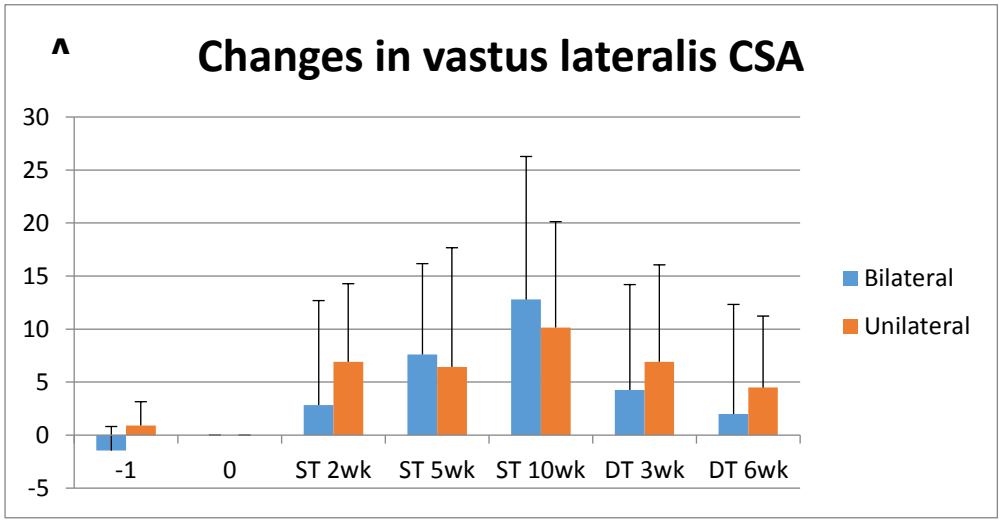


FIGURE 17. Comparing Unilateral vs Bilateral changes in CSA for the VL. Data presented as mean ± 95% CI.

There were no observed significant differences for I/O values in unilateral or bilateral TMS measurements. This is also seen in SICI, ICF and SP measurements (Table 1). No trends were seen irrespective of significance.

TABLE 1. Unilateral vs Bilateral TMS results. Data presented as mean ± 95% CI.

	0	**2**	**5**	**10**	**D3**	**D6**
I-O Curve						
Unilateral	0.330± 0.203	0.298± 0.189	0.267± 0.209	0.219± 0.173	0.360± 0.234	0.306± 0.198
Bilateral	0.215± 0.100	0.241± 0.105	0.171± 0.068	0.180± 0.100	0.292± 0.245	0.210± 0.111
No differences were observed for interaction effects of time by condition (F = 1.52 P = 0.84)						
SICI						
Unilateral	0.643± 0.270	0.663± 0.302	0.623± 0.250	0.655± 0.303	0.606± 0.209	0.715± 0.302
Bilateral	0.618± 0.173	0.661± 0.264	0.614± 0.167	0.688± 0.352	0.669± 0.203	0.643± 0.232
No differences were observed for interaction effects of time by condition (F = 1.14, P = 0.53)						
ICF						
Unilateral	0.979± 0.108	1.040± 0.216	1.106± 0.205	1.061± 0.208	0.948± 0.314	1.099± 0.234
Bilateral	0.990± 0.180	1.196± 0.268	1.009± 0.263	1.140± 0.392	0.886± 0.245	1.018± 0.271
No differences were observed for interaction effects of time by condition (F = 0.37, P = 0.62)						
SP (ms)						
Unilateral	0.107± 0.015	0.118± 0.019	0.123± 0.018	0.111± 0.018	0.105± 0.012	0.110± 0.020
Bilateral	0.113± 0.023	0.124± 0.023	0.125± 0.022	0.101± 0.018	0.100± 0.013	0.099± 0.015
No differences were observed for interaction effects of time by condition (F = 0.43, P = 0.66)						

8. DISCUSSION

In response to the hypertrophy training protocol force of the quadriceps and cross sectional area significantly increased over the training period. It was also found that the MEP Amplitude was reduced over the training procol but then increased again during the detraining period. the study found no significant differences as a result of unilateral vs bilateral training responses.

Force

Force significantly increased from pre to post measurements as well as decreased from post to detraining week 3. These results are shared significantly over the majority of studies as seen in Ahtianen et al., (2003) observed a 20.9% increase in maximal force output following a 21 week strength training program. Narici et al., (1989) also found average increases of 24.8% increases in MVC following a 60 day strength training program. The effects of a strength training on force have been extensively investigated, particularly in the concentric part of the movement (Cardinale et al. 2011, 106) and the current study provides no except to the well established knowledge. Interestly, it has been reported that muscle strength increases in response to the velocity trained (Aagaard et al., 1994), although it has been previously shown to also improve muscle strength at lower velocities of that trained (Coyle et al., 1981) as well as higher (Aagaard et al., 1994).

Cross Sectional Area

A significant increase of 11% in CSA from pre measurements to post measurements in the vastus lateralis as a result of the study. The CSA area then again reduced from post to detraining although still remained larger than originally observed. Similarly, Narici et al., (1989) found that after 60 days of strength training they saw increases of 8% in quadriceps, they also found the following the detraining period changes had a similar time course to those during training. Narici et al., (1996) also established an increase of 13-18% increase (depending on quadriceps region) in CSA following a weight training protocol. Likewise Young et al, (1983) also found a 6% increase in CSA following high resistance strength trainingin the quadriceps. Equally, in a review article Wernbom et al., (2007) revealed that typically when observing the increase in muscle CSA of the quadriceps after training it usually results in 6-9% increases when strength training in completed within untrained subjects. While these increases in cross sectional area accound for some of the increases in force there is still a large percentage unaccounted for.

Input/output curve

The main finding presented from the results section was that MEP Amplitude was reduced as the hypertrophy program progressed. The effect following the period of detraining revealed a sharp spike in MEP Amplitude following a plateau back to normal levels after 6 weeks of detraining. The initial part of these results are in line with Jensen et al., (2005) when testing the effects of skill training three times a week for four weeks on MEP size they found that maximal MEP and input/output curve decreased. Likewise, Carroll et al. (2001) found that increases in force from a 4 week strength program resulted in a reduction in corticospinal excitability. On the other hand Kidgell and Pearce (2010) found that following a 4 week strength training intervention on the FDI in the hand results in large increases in strength in the absence of increases in corticospinal excitability. Several other short term 4 week strength studies have been conducted (Griffin & Cafarelli, 2007, Beck et al. 2007, Schubert et al. 2008 and Hortobagyi et al. 2009) in which some reveal no clear alterations in MEP size even though reporting an increase in MVC, while others suggest increases in corticospinal excitability (Griffin & Cafarelli 2007, Beck et al. 2007) who suggested that the increase in MEP amplitude was due to the increasing size of the descending corticospinal volley leading to greater activation of the motor unit. Inconsistent results can accumulate from variations in muscle groups studied or the condition in which the muscle has been tested for example active or passive (Carroll et al., 2011). However these methods significantly differ from the present study as a result of the length of the strength training program.

Furthermore, Latella et al., (2012) studied the effects of an 8 week unilateral strength training program on MVC and corticospinal pathways. They revealed that no significant MEP amplitude changes were found, these results have been suggested because of the nature of the neural pathways in which adaption is movement specific as in the current study unilateral leg press was trained in a dynamic condition whereas it was tested in an isometric condition. When testing the reliability of the input-output curve Carroll et al., (2001) found that it appears to be a reliable method to measure the longitudinal examination of the corticospinal pathway.

SICI/ICF

When exploring cortical and spinal excitability considerations must be made for the influence of inhibition or facilitation, more specifically SICI and ICF. While the muscle is activated SICI is reduced, although increased in the extensor muscle (Daskalakis et al. 2002). Evidence that SICI is controlled by cortical inhibitory interneurons includes an absence of change at the spinal level, a failure to suppress the response to double transcranial stimulation and noted

reduction in the corticospinal waves evoked by TMS (Daskalakis et al., 2002). Conversely, other findings suggest SICI is more related to GABAergic receptors (Daskalakis et al., 2002).

More specifically, SICI is resulted from pairing a subthreshold conditioning stimulus with a suprathreshold test stimulus at intervals of 1-5ms which inhibits the MEP produced by the test stimulus. Similarly, ICF involves the pairing of a subthreshold and suprathreshold stimulus although they are completed with an interval of 10-15ms. In the present study SICI and ICF results did not reveal any significant changes or trends. Likewise, Beck et al., (2007) reported an increase in the strength changes following a ballistic training program which did not include changes associated with SICI and ICF suggesting that adaptations were expected to take place at the supraspinal level. Equally, Stevens-Lapsleyet et al. (2013), when comparing corticospinal excitability between older and younger groups found that there were no significant differences in intracortical excitability when observed with SICI. These results are in contrast with Goodwill et al., (2012) as they found while training unilateral strength that subject in the trained leg revealed a 24.5% reduction in SICI in the trained leg and a 21.3% reduction in the untrained leg when compared to baseline values. The changes observed may be as a result of task dependant changes with motor skill acquisition as has been previously mentioned although primarily in hand muscles. Likewise Perez et al., (2004) studied the effects of motor skill training on inhibition and facilitation. They found SICI was significantly reduced while ICF remained the same suggesting SICI contains a functional role during complex tasks while ICF remains sensitive to simple movements.

Furthermore, Smith et al. (2014), revealed that there were no changes in corticospinal excitability although there was a significant reduction in SICI following a bout of exhaustive exercise when compared to baseline values, providing evidence to suggest that GABAa is reduced in a single bout of exercise proposing that there may be acute and chronic increases in neuroplasticity with exercise.

SP

The silent period is the elicited suppression of ongoing motor activity after TMS-evoked muscle response during target muscle activation (Fuhr at al. 1991). Mechanisms are currently not so well understood but it is accepted that the initial part is spinal and the latter part has cortical origin (Fuhr at al. 1991). Generally a higher amplitude in the MEP results in a larger SP being produced and there is high inter variability although repeatable within subject. Currently literature suggests a couple of ways to measure the SP but there is no current

consensus as to which methodology is the most adequate (Säisänen et al. 2008). The present study found no significant changes within the cortical silent period although it may be noted that as MEP amplitude decreases SP increases and as the MEP amplitude increases, the SP decreases.

In contrast to these results Latella et al., (2012), found during an 8 week unilateral strength training program there was a reduction in the SP duration, these results correspond with Kidgell and Pearce (2010) who also saw a reduction is SP duration following a short strength-training program. Although the exact mechanisms for this reduction is unknown it is said to be because of the decreased inhibitory input to the motorneuron pool leading to suggest that the increase of strength may be due to the overall increased excitability of the corticospinal pathway.

Unilateral Vs Bilateral

Interestingly, the present study when comparing the results of the bi and unilateral groups showed no significant differences or changes in response to hypertrophy training. There we no significant differences when comparing the two groups in the current study, this is in line with Goodwill et al., (2012) who observed that when implementing a unilateral strength program both legs reacted similarly to TMS measurements particularly SICI even though one was trained. These results are reinforced by Latella et al., (2012), who also observed corticospinal inhibition following unilateral strength training. They found EMG and corticospinal exicitability to be unchanged in both legs from baseline values while strength values increased and corticospinal inhibition was significantly reduced. This supports the notion of corticospinal adaptations underpinning gains in the lower limbs following unilateral strength training are cross-educational (Latella et al., 2012). Lee et al., (2009) supports this cross education when observing voluntary activation of the untrained limb after unilateral strength training. They found that although small but still significant, the untrained limb increased in voluntary activation.

Strengths & Limitations

When compared with many other previous studies in this field this study has a large sample size (n=26). Furthermore it was similar to other studies methodologically when attempting to oberseve neural adaptations in response to resistance training (Griffin & Cafarelli, 2007; Latella et al., 2012; Beck et al., 2007; Stevens-Lapsleyet et al., 2013; Goodwill et al., 2012). There are limitations as a result of utilising TMS and EMG which have been previously mentioned.

9. CONCLUSION

The present study revealed a decrease in corticospinal excitability during the training program, followed by a sharp increase after three weeks of detraining and then finally reducing again to baseline values after six weeks of detraining. These results suggest the importance of recovery in order to allow for positive adaptation to hypertrophy training within corticospinal excitability. The hypothesis addressing the extent of the supraspinal inhibitory processes from the current thesis has very little contribution although other results may differ for this.

Nevertheless, forthcoming studies must better determine the site of the adaptation within corticospinal excitability, but not only taking a supraspinal approach but also further at the spinal effects over a longer period of time than most have currently been studied.

10. REFERENCES

1 Aagaard, P., Simonsen, E. B., Andersen, J. L., Magnusson, P., & Dyhre-Poulsen, P. (2002). Neural adaptation to resistance training: changes in evoked V-wave and H-reflex responses. *Journal of Applied Physiology*, *92*(6), 2309-2318.

2 Aagaard, P., Simonsen, E. B., Andersen, J. L., Magnusson, S. P., Halkjaer-Kristensen, J., & Dyhre-Poulsen, P. (2000). Neural inhibition during maximal eccentric and concentric quadriceps contraction: effects of resistance training. *Journal of Applied Physiology*, *89*(6), 2249-2257.

3 Aagaard, P., Simonsen, E. B., Trolle, M., Bangsbo, J., & Klausen, K. (1994). Effects of different strength training regimes on moment and power generation during dynamic knee extensions. *European journal of applied physiology and occupational physiology*, *69*(5), 382-386.

4 Ahtiainen, J. P., Pakarinen, A., Alen, M., Kraemer, W. J., & Häkkinen, K. (2003). Muscle hypertrophy, hormonal adaptations and strength development during strength training in strength-trained and untrained men. *European journal of applied physiology*, *89*(6), 555-563.

5 Arai, N., Okabe, S., Furubayashi, T., Terao, Y., Yuasa, K., & Ugawa, Y. (2005). Comparison between short train, monophasic and biphasic repetitive transcranial magnetic stimulation (rTMS) of the human motor cortex. *Clinical Neurophysiology*, *116*(3), 605-613.

6 Avela, J., & Gruber, M. (2010). Transcranial magnetic stimulation as a tool to study the role of the motor cortex in human muscle function. *Neuromuscular Aspects of Sport Performance*, *17*, 115-134.

7 Behrens, M., Mau-Moeller, A., & Bruhn, S. (2012). Effect of exercise-induced muscle damage on neuromuscular function of the quadriceps muscle. *International journal of sports medicine*, *33*(08), 600-606.

8 Beck, S., Taube, W., Gruber, M., Amtage, F., Gollhofer, A., & Schubert, M. (2007). Task-specific changes in motor evoked potentials of lower limb muscles after different training interventions. *Brain research*, *1179*, 51-60.

9 Buresh, R., Berg, K., & French, J. (2009). The effect of resistive exercise rest interval on hormonal response, strength, and hypertrophy with training. *The Journal of Strength & Conditioning Research*, *23*(1), 62-71.

10 Butler, J. E., Taylor, J. L., & Gandevia, S. C. (2003). Responses of human motoneurons to corticospinal stimulation during maximal voluntary contractions and ischemia. *Journal of Neuroscience*, *23*(32), 10224-10230.

11 Cannon, R. J., & Cafarelli, E. (1987). Neuromuscular adaptations to training. *Journal of Applied Physiology*, *63*(6), 2396-2402.

12 Cardinale, M., Newton, R., & Nosaka, K. (Eds.). (2011). *Strength and conditioning: biological principles and practical applications*. John Wiley & Sons.

13 Carroll, T. J., Riek, S., & Carson, R. G. (2001). Reliability of the input–output properties of the cortico-spinal pathway obtained from transcranial magnetic and electrical stimulation. *Journal of neuroscience methods*, *112*(2), 193-202.

14 Carroll, T. J., Selvanayagam, V. S., Riek, S., & Semmler, J. G. (2011). Neural adaptations to strength training: moving beyond transcranial magnetic stimulation and reflex studies. *Acta physiologica*, *202*(2), 119-140.

15 Challis, J. H. (2000). Muscle-tendon architecture and athletic performance. *Biomechanics in Sport (Olympic Encyclopaedia of Sports Medicine Vol. IX)*, 33-55.

16 Chen, R., Lozano, A. M., & Ashby, P. (1999). Mechanism of the silent period following transcranial magnetic stimulation evidence from epidural recordings. *Experimental brain research*, *128*(4), 539-542.

17 Clark, B. C., Taylor, J. L., Hoffman, R. L., Dearth, D. J., & Thomas, J. S. (2010). Cast immobilization increases long-interval intracortical inhibition. *Muscle & nerve*, *42*(3), 363-372.

18 Cote, C., Simoneau, J. A., Lagasse, P., Boulay, M., Thibault, M. C., Marcotte, M., & Bouchard, C. (1988). Isokinetic strength training protocols: do they induce skeletal muscle fiber hypertrophy?. *Archives of physical medicine and rehabilitation*, *69*(4), 281-285.

19 Coyle, E. F., Feiring, D. C., Rotkis, T. C., Cote 3rd, R. W., Roby, F. B., Lee, W., & Wilmore, J. H. (1981). Specificity of power improvements through slow and fast isokinetic training. *Journal of applied physiology*, *51*(6), 1437-1442.

20 Daskalakis, Z. J., Christensen, B. K., Fitzgerald, P. B., Roshan, L., & Chen, R. (2002). The mechanisms of interhemispheric inhibition in the human motor cortex. *The Journal of physiology*, *543*(1), 317-326.

21 Del Balso, C., & Cafarelli, E. (2007). Adaptations in the activation of human skeletal muscle induced by short-term isometric resistance training. *Journal of Applied Physiology*, *103*(1), 402-411.

22 Devanne, H., Lavoie, B. A., & Capaday, C. (1997). Input-output properties and gain changes in the human corticospinal pathway. *Experimental brain research*, *114*(2), 329-338.

23 Di Lazzaro, V., Restuccia, D., Oliviero, A., Profice, P., Ferrara, L., Insola, A., ... & Rothwell, J. C. (1998). Magnetic transcranial stimulation at intensities below active motor threshold activates intracortical inhibitory circuits. *Experimental Brain Research*, *119*(2), 265-268.

24 Duchateau, J., & Baudry, S. (2010). Training adaptation of the neuromuscular system. *Neuromuscular aspects of sport performance*, *17*, 216-253.

25 Enoka, R. M. (2008). *Neuromechanics of human movement*. Human kinetics.

26 Farina, D., Holobar, A., Merletti, R., & Enoka, R. M. (2010). Decoding the neural drive to muscles from the surface electromyogram. *Clinical neurophysiology*, *121*(10), 1616-1623.

27 Farina, D., Merletti, R., & Enoka, R. M. (2004). The extraction of neural strategies from the surface EMG. *Journal of applied physiology*, *96*(4), 1486-1495.

28 Fry, A. C. (2004). The role of resistance exercise intensity on muscle fibre adaptations. *Sports medicine*, *34*(10), 663-679.

29 Fuhr, P., Agostino, R., & Hallett, M. (1991). Spinal motor neuron excitability during the silent period after cortical stimulation. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *81*(4), 257-262.

30 Gandevia, S. C. (2001). Spinal and supraspinal factors in human muscle fatigue. *Physiological reviews*, *81*(4), 1725-1789.

31 Gangitano, M., Valero-Cabré, A., Tormos, J. M., Mottaghy, F. M., Romero, J. R., & Pascual-Leone, Á. (2002). Modulation of input–output curves by low and high frequency repetitive transcranial magnetic stimulation of the motor cortex. *Clinical Neurophysiology*, *113*(8), 1249-1257.

32 Goodwill, A. M., Pearce, A. J., & Kidgell, D. J. (2012). Corticomotor plasticity following unilateral strength training. *Muscle & nerve*, *46*(3), 384-393.

33 Griffin, L., & Cafarelli, E. (2007). Transcranial magnetic stimulation during resistance training of the tibialis anterior muscle. *Journal of Electromyography and Kinesiology*, *17*(4), 446-452.

34 Hallett, M. (2000). Transcranial magnetic stimulation and the human brain. *Nature*, *406*(6792), 147-150.

35 Hortobágyi, T., & Maffiuletti, N. A. (2011). Neural adaptations to electrical stimulation strength training. *European journal of applied physiology*, *111*(10), 2439-2449.

36 Jensen, J. L., Marstrand, P. C., & Nielsen, J. B. (2005). Motor skill training and strength training are associated with different plastic changes in the central nervous system. *Journal of applied physiology*, *99*(4), 1558-1568.

37 Jones, D. A., & Rutherford, O. M. (1987). Human muscle strength training: the effects of three different regimens and the nature of the resultant changes. *The Journal of physiology*, *391*(1), 1-11.

38 Kalmar, J. M., & Cafarelli, E. (2006). Central excitability does not limit postfatigue voluntary activation of quadriceps femoris. *Journal of Applied Physiology*, *100*(6), 1757-1764.

39 Kandel, E. R. (2000). Learning and memory. *Principles of neural science*, 1227-1246.

40 Kent-Braun, J. A. (1999). Central and peripheral contributions to muscle fatigue in humans during sustained maximal effort. *European journal of applied physiology and occupational physiology*, *80*(1), 57-63.

41 Kidgell, D. J., & Pearce, A. J. (2010). Corticospinal properties following short-term strength training of an intrinsic hand muscle. *Human movement science*, *29*(5), 631-641.

42 Kraemer, W. J., Adams, K., Cafarelli, E., Dudley, G. A., Dooly, C., Feigenbaum, M. S., ... & Newton, R. U. (2002). American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Medicine and science in sports and exercise*, *34*(2), 364-380.

43 Latella, C., Kidgell, D. J., & Pearce, A. J. (2012). Reduction in corticospinal inhibition in the trained and untrained limb following unilateral leg strength training. *European journal of applied physiology*, *112*(8), 3097-3107.

44 Lee, M., Gandevia, S. C., & Carroll, T. J. (2009). Unilateral strength training increases voluntary activation of the opposite untrained limb. *Clinical Neurophysiology*, *120*(4), 802-808.

45 Lee, M., Gandevia, S. C., & Carroll, T. J. (2009). Short-term strength training does not change cortical voluntary activation. *Medicine and science in sports and exercise*, *41*(7), 1452-1460.

46 Mau-Moeller, A., Behrens, M., Lindner, T., Bader, R., & Bruhn, S. (2013). Age-related changes in neuromuscular function of the quadriceps muscle in physically active adults. *Journal of Electromyography and Kinesiology*, *23*(3), 640-648.

47 McGinley, M., Hoffman, R. L., Russ, D. W., Thomas, J. S., & Clark, B. C. (2010). Older adults exhibit more intracortical inhibition and less intracortical facilitation than young adults. *Experimental gerontology*, *45*(9), 671-678.

48 Narici, M. V., Hoppeler, H., Kayser, B., Landoni, L., Claassen, H., Gavardi, C., ... & Cerretelli, P. (1996). Human quadriceps cross-sectional area, torque and neural activation during 6 months strength training. *Acta Physiologica Scandinavica*, *157*(2), 175-186.

49 Narici, M. V., Roi, G. S., Landoni, L., Minetti, A. E., & Cerretelli, P. (1989). Changes in force, cross-sectional area and neural activation during strength training and detraining of the human quadriceps. *European journal of applied physiology and occupational physiology*, *59*(4), 310-319.

50 Palmieri, R. M., Ingersoll, C. D., & Hoffman, M. A. (2004). The Hoffmann reflex: methodologic considerations and applications for use in sports medicine and athletic training research. *Journal of athletic training*, *39*(3), 268.

51 Pascual-Leone, A., Davey, N. J., Rothwell, J., Wasserman, E. M., & Puri, B. K. (Eds.). (2002). *Handbook of transcranial magnetic stimulation*. Arnold.

52 Pearcey, G. E., Power, K. E., & Button, D. C. (2014). Differences in supraspinal and spinal excitability during various force outputs of the biceps brachii in chronic-and non-resistance trained individuals. *PloS one*, *9*(5), e98468.

53 Perez, M. A., Lungholt, B. K., Nyborg, K., & Nielsen, J. B. (2004). Motor skill training induces changes in the excitability of the leg cortical area in healthy humans. *Experimental brain research*, *159*(2), 197-205.

54 Philpott, D. T., Pearcey, G. E., Forman, D., Power, K. E., & Button, D. C. (2015). Chronic resistance training enhances the spinal excitability of the biceps brachii in the non-dominant arm at moderate contraction intensities. *Neuroscience letters*, *585*, 12-16.

55 Pitcher, J. B., Ogston, K. M., & Miles, T. S. (2003). Age and sex differences in human motor cortex input–output characteristics. *The Journal of physiology*, *546*(2), 605-613.

56 Rainoldi, A., & Gazzoni, M. (2011). Neuromuscular physiology.

57 Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & Safety of TMS Consensus Group. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical neurophysiology*, *120*(12), 2008-2039.

58 Roy, F. D., & Gorassini, M. A. (2008). Peripheral sensory activation of cortical circuits in the leg motor cortex of man. *The Journal of physiology*, *586*(17), 4091-4105.

59 Säisänen, L., Julkunen, P., Niskanen, E., Danner, N., Hukkanen, T., Lohioja, T., ... & Könönen, M. (2008). Motor potentials evoked by navigated transcranial magnetic stimulation in healthy subjects. *Journal of clinical neurophysiology*, *25*(6), 367-372.

60 Säisänen, L., Pirinen, E., Teitti, S., Könönen, M., Julkunen, P., Määttä, S., & Karhu, J. (2008). Factors influencing cortical silent period: optimized stimulus location, intensity and muscle contraction. *Journal of neuroscience methods*, *169*(1), 231-238.

61 Schoenfeld, B. J. (2010). The mechanisms of muscle hypertrophy and their application to resistance training. *The Journal of Strength & Conditioning Research*, *24*(10), 2857-2872.

62 Schieber, M. H. (2004). Motor control: basic units of cortical output. *Current Biology*, *14*(9), R353-R354.

63 Schubert, M., Beck, S., Taube, W., Amtage, F., Faist, M., & Gruber, M. (2008). Balance training and ballistic strength training are associated with task-specific corticospinal adaptations. *European Journal of Neuroscience*, *27*(8), 2007-2018.

64 Smith, A. E., Goldsworthy, M. R., Garside, T., Wood, F. M., & Ridding, M. C. (2014). The influence of a single bout of aerobic exercise on short-interval intracortical excitability. *Experimental brain research*, *232*(6), 1875-1882.

65 Spira, M. E., Yarom, Y., & Parnas, I. (1976). Modulation of spike frequency by regions of special axonal geometry and by synaptic inputs. *Journal of neurophysiology*, *39*(4), 882-899.

66 Stevens-Lapsley, J. E., Thomas, A. C., Hedgecock, J. B., & Kluger, B. M. (2013). Corticospinal and intracortical excitability of the quadriceps in active older and younger healthy adults. *Archives of gerontology and geriatrics*, *56*(1), 279-284.

67 Tallent, J., Goodall, S., Hortobágyi, T., Gibson, A. S. C., French, D. N., & Howatson, G. (2012). Repeatability of corticospinal and spinal measures during lengthening and shortening contractions in the human tibialis anterior muscle. *PloS one*, *7*(4), e35930.

68 Thorstensson, A., Karlsson, J., Viitasalo, J. H. T., Luhtanen, P., & Komi, P. V. (1976). Effect of strength training on EMG of human skeletal muscle. *Acta Physiologica Scandinavica*, *98*(2), 232-236.

69 Toigo, M., & Boutellier, U. (2006). New fundamental resistance exercise determinants of molecular and cellular muscle adaptations. *European journal of applied physiology*, *97*(6), 643-663.

70 Wagle-Shukla, A., Ni, Z., Gunraj, C. A., Bahl, N., & Chen, R. (2009). Effects of short interval intracortical inhibition and intracortical facilitation on short interval intracortical facilitation in human primary motor cortex. *The Journal of physiology*, *587*(23), 5665-5678.

71 Ward, S. H., Pearce, A., Bennell, K. L., Peitrosimone, B., & Bryant, A. L. (2016). Quadriceps cortical adaptations in individuals with an anterior cruciate ligament injury. *The Knee*, *23*(4), 582-587.

72 Wassermann, E. M., Samii, A., Mercuri, B., Ikoma, K., Oddo, D., Grill, S. E., & Hallett, M. (1996). Responses to paired transcranial magnetic stimuli in resting, active, and recently activated muscles. *Experimental Brain Research*, *109*(1), 158-163.

73 Weier, A. T., Pearce, A. J., & Kidgell, D. J. (2012). Strength training reduces intracortical inhibition. *Acta physiologica*, *206*(2), 109-119.

74 Wernbom, M., Augustsson, J., & Thomeé, R. (2007). The influence of frequency, intensity, volume and mode of strength training on whole muscle cross-sectional area in humans. *Sports medicine*, *37*(3), 225-264.

75 Zehr, P. E. (2002). Considerations for use of the Hoffmann reflex in exercise studies. *European journal of applied physiology*, *86*(6), 455-468.

76 Ziemann, U., Netz, J., Szelényi, A., & Hömberg, V. (1993). Spinal and supraspinal mechanisms contribute to the silent period in the contracting soleus muscle after transcranial magnetic stimulation of human motor cortex. *Neuroscience letters*, *156*(1-2), 167-171.

Appendicies

Intervention training program		Week 41	Rest	Week 42	Week 43
Three medium weeks, four hard weeks, and three medium weeks.					
The volume of training will increase over the first seven weeks, then the volume will		Tuesday/Wednesday		Tuesday/Wednesday	Tuesday/Wednesday
decrease and the training intensity will increase. Training volume is equal for both groups.					
Unilateral group will have in main movements between limbs		Dynamic leg press 5x10xRM		Isometric leg press testing.	Dynamic leg press 5x10xRM
2-3 min rest, in accessory movements without the rest between the limbs.		Isometric knee extensors (90deg.) 2x60s(5s work + 15s rest)		Isometric knee extensors testing.	Isometric knee extensors (90deg.) 2x60s(5s work + 15s rest)
Rest time between sets stays the same during the whole program.		Isometric knee flexors (90deg.) 2x60s(5s work + 15s rest)		Dynamic leg press 5x10xRM	Isometric knee flexors (90deg.) 2x60s(5s work + 15s rest)
Friday subjects will start from legs and move on to the upper body.		Three rounds of core work		Isometric leg press testing.	Three rounds of core work
Sunday it will be vice versa to minimize the order effect.				Isometric knee extensors testing.	
During the intervention subjects will have protein/CHO supplement after every workout.				Isometric knee extensors (90deg.) 2x60s(5s work + 15s rest)	
				Isometric knee flexors (90deg.) 2x60s(5s work + 15s rest)	
				Three rounds of core work	
Friday					
Leg press: Bil. + Uni		3x10x70%	3min	4x10x70%	5x10x70%
Knee ext.: Bil. + Uni		3x12x60%	1min	3x8x70%	3x12x65%
Knee flex. Laying down: Bil. + Uni		3x12x60%	1min	3x8x70%	3x12x65%
Dumbell benchpress: Bil. + Uni		3x10x50% from BP	3min	4x10x50% from BP	5x10x50% from BP
Seated french press with DB: Bil. + Uni.		-		2x10x60%	1x10x60%, 2x10xRM
Horizontal row with narrow grip: Bil. + Uni		3x12x60%	90s	3x8x70%	3x12x65%
Plank + isometric back extension		2x45 s + 10	1min	2x45 s + 10	3x45 s + 10
Sunday					
Bench press done in smith: Bil. + Uni		3x10x70%	3-4min	4x10x70%	5x10x70%
Horizontal row with narrow grip: Bil. + Uni		3x12x60%	90s	3x8x70%	3x12x65%
Zotmann curl with dumbell: Bil. + Uni		3x12x60%	60s	3x12x60%	3x12x60%
Leg press: Bil. + Uni		3x10x70%	3-4min	4x10x70%	5x10x70%
Knee extensors : Bil. + Uni		3x12x60%	1min	3x8x70%	3x12x65%
Knee flexors: Bil. + Uni		3x12x60%	1min	3x8x70%	3x12x65%
Seated abdominals		2x10	0-1min	3x10	4x10

	Week 44		Week 45		Week 46		Week 47
			In the lab:				
	Tuesday/Wednesday				Tuesday/Wednesday		Tuesday/Wednesday
			MID TESTS				
	Isometric leg press testing				Isometric leg press testing		Dynamic leg press 5x10xRM
	isometric knee extensors testing				isometric knee extensors testing		Isometric knee extensors (90deg.) 2x60s(5s work + 15s rest)
	Dynamic leg press 5x10xRM				Dynamic leg press 5x10xRM		Isometric bench press (90deg.) 2x60s(5s work + 15s rest)
	Isometric leg press testing				Isometric leg press testing		Knee flexors 3x12x70%
	isometric knee extensors testing				isometric knee extensors testing		Lat pulldown 3x12x70%
	Isometric knee extensors (90deg.) 2x60s(5s work + 15s rest)				Isometric knee extensors (90deg.) 2x60s(5s work + 15s rest)		Superman - core exercise 3x10
	Isometric knee flexors (90deg.) 2x60s(5s work + 15s rest)				Isometric bench press (90deg.) 2x60s(5s work + 15s rest)		
	Three rounds of core work				Knee flexors 3x12x70%		
					Lat pulldown 3x12x70%		
					Superman - core exercise 3x10		
Friday							
Leg press: Bil. + Uni	5x5x80%		6x6x85%		5x4x90%		4x3x95%, 15xRM(70%)
Knee ext.: Bil. + Uni	3x12x65%		-		3x10x70%		3x12x70%
Stiff legged deadlift with DB: Bil. + Uni	3x12x60%		3x8x65%		3x10x70%		3x12x70%
Dumbell benchpress with stop: Bil. + Uni	3x10x70%		4x10x70%		3x8x72,5%		2x5x75%, 15xRM (60%)
Seated french press with db: Bil. + Uni.	2x12x60%		-		4x8x70%		4x8x70%
Horizontal row with wide grip: Bil. + Uni	3x12x65%		3x12x65%		3x10x70%		3x12x70%
Seated abdominals	3x10		3x12		3x15		3x20
Sunday							
Bench press done in smith: Bil. + Uni	5x5x80%		6x4x85%		5x4x90%		4x3x95%, 15xRM(65%)
Seated overhead press in machine Bil. + Uni.	1x12x50%		3x12x50%		3x10x50%		3x12x50%
Zotmann curl with dumbell: Bil. + Uni	-		2x12x50%		2x15x50%		3x15x50%
Row with dumbell in incline bench: Bil. + Uni.	2x12x65%		3x8x70%		3x10x70%		3x12x70%
Triceps push down: Bil. + Uni	2x12x65%		3x8x70%		3x10x70%		3x12x70%
Leg press one and half rep. Bil. + Uni	2x8x50%		3x8x55%		3x6x60%		4x6x70%
Knee flexors: Bil. + Uni	-		3x8x70%		3x10x70%		3x12x70%
Side plank + Dynamic back extensions	3x30 s per side + 10		3x30 s per side + 10		3x30 s per side + 15		3x30 s per side + 15

	Week 48		Week 49		Week 50
	Tuesday/Wednesday		Tuesday/Wednesday		Tuesday/Wednesday
	Dynamic leg press 5x10xRM		Dynamic leg press 5x10xRM		Isometric leg press testing
	Isometric knee extensors (90deg.) 2x60s(5s work + 15s rest)		Isometric knee extensors (90deg.) 2x60s(5s work + 15s rest)		isometric knee extensors testing
	Isometric bench press (90deg.) 2x60s(5s work + 15s rest)		Isometric bench press (90deg.) 2x60s(5s work + 15s rest)		Dynamic leg press 5x10xRM
	Knee flexors 3x12x70%		Knee flexors 3x12x70%		Isometric leg press testing
	Lat pulldown 3x12x70%		Lat pulldown 3x12x70%		isometric knee extensors testing
	Superman - core exercise 3x10		Superman - core exercise 3x10		Isometric knee extensors (90deg.) 2x60s(5s work + 15s rest)
					Isometric bench press (90deg.) 2x60s(5s work + 15s rest)
					Knee flexors 3x12x70%
					Lat pulldown 3x12x70%
					Superman - core exercise 3x10
Friday					
	Leg press max tests (New training weights):				
Leg press: Bil. + Uni	4x6x80%		4x8x80%		2x6x90%
Knee ext.: Bil. + Uni	3x6x80%		4x8x80%		1x10x85%
Stiff legged deadlift with DB: Bil. + Uni	3x6x80%		3x8x80%		3x8x80%
Dumbell benchpress with 6s eccentric phase	4x6x80%		4x8x80%		3x6x80%
Dumbell incline benchpress			2x6x70%		2x6x70%
Horizontal row with narrow grip: Bil. + Uni	3x6x80%		3x8x80%		3x8x80%
Plank + isometric back extensions 5kg	3x45 s + 10		3x45 s + 10		3x45 s + 10
Sunday					
	Bench press max tests (New training weights):				
Bench press done in smith: Bil. + Uni	4x6x80%		4x8x80%		2x6x90%
Biceps curl with dumbell: Bil. + Uni	3x12x50%		3x12x50%		3x12x50%
Seated overhead press in machine Bil. + Uni.	2x10x50%		2x10x50%		-
Triceps push down 1s hold in lock position: Bil. + Uni	3x6x80%		3x8x80%		3x6x80%
Leg press with 6s eccentric phase: Bil. + Uni	4x6x70%		4x8x70%		-
Knee extensors: Bil. + Uni	3x6x80%		2x20RM(65%)		3x8x80%
Side plank + Dynamic back extensions	3x30 s per side + 10		3x30 s per side + 10		3x30 s per side + 10