MOTOR UNIT ACTIVITY AND NEUROMUSCULAR FUNCTION AFTER EXERCISE-INDUCED DAMAGE TO ELBOW FLEXOR MUSCLES

A thesis submitted for the Degree of

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by

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Abstract

It has been known for some time that eccentric exercise produces significant muscle damage resulting in changes in muscle structure and function, leading to a fall in maximal force production, a rise in passive tension, as well as delayed-onset muscle soreness. The majority of studies to date have focussed on examining the structural changes in the muscle, however, little is known about how the nervous system responds to eccentric exercise-induced muscle damage. This thesis has investigated for the first time changes at the level of single motor unit activity following eccentric exercise, which provides specific information about the activity of spinal motor neurons that can reveal details of the nature of the neural adaptations to repeated eccentric contractions.

Muscle damage was induced in experiments in Chapters 2 and 3 by controlled lowering of a hand-held load, requiring eccentric contraction of the elbow flexor muscles, and in Chapter 4, by maximal voluntary eccentric contractions of the elbow flexors on an isokinetic dynamometer, to induce a 40% reduction in MVC force in all subjects. As well as an extended reduction in MVC force, I found consistent with results from previous studies a reduction in relaxed elbow joint angle (indicative of a rise in passive tension) up to 24-hrs after the exercise and delayed-onset muscle soreness a day later. An increase in sub-maximal biceps brachii EMG activity and increased force fluctuations for up to 24-hrs after the exercise was also found, along with increased antagonist activity from triceps brachii EMG immediately after eccentric exercise, confirming results from other studies.

Following a single bout of eccentric exercise, I found an increase in correlated motor unit activity (motor unit synchronization and coherence; Chapter 2) and a reduction in the force at which motor units were recruited (Chapter 3) that lasted for at least 24 hours after the

exercise. Minimum motor unit discharge rates were also influenced by eccentric exercise, but had recovered 24 hours later (Chapter 3). These findings indicate that eccentric exercise-induced muscle damage alters the correlated discharge behaviour and recruitment threshold of human motor units in elbow flexor muscles for ≤ 24 hrs. It was therefore hypothesised in Chapter 4 that a lasting adaptation in correlated motor unit activity and/or motor unit recruitment may contribute to the "repeated bout effect", which results in reduced muscle damage from a subsequent bout of eccentric exercise.

In Chapter 4, a repeated bout of eccentric exercise performed 7 days after the initial bout resulted in reduced symptoms of muscle damage, including a faster recovery of muscle strength, and reduced development of muscle soreness. Motor unit activity measured 7 days after the initial bout of exercise (immediately before the repeated bout) showed elevated motor unit synchronization, but a recovery of motor unit recruitment threshold to pre-exercise levels. These findings are the first to demonstrate a long-term neural adaptation following eccentric exercise, and suggest a potential role for motor unit synchronization in reducing muscle damage after a repeated bout of eccentric exercise.

Declaration

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1. Literature Review

1.1. Introduction

An eccentric contraction occurs when a contracting muscle is forcibly lengthened (Proske and Allen 2005; Proske and Morgan 2001) and is present in everyday activities such as downhill walking, running and lowering of an object. For example, during downhill walking the quadriceps lengthens during knee extension to prevent falling down the hill (Proske et al. 2004). Unlike other types of exercise such as concentric or isometric, eccentric exercise is known to produce significant muscle damage. Muscle damage reduces the total force that can be produced by the muscle, along with shifting the muscle's length-tension relation to longer muscle lengths for peak force production, and producing muscle soreness a day later. Recently, eccentric exercise has also been shown to alter the neural control of force by increasing the relative muscle activity produced during sub-maximal contractions (as recorded by electromyography (EMG)), and decreasing the ability of the muscle to maintain a steady force (increased force fluctuations) about a target. However, the possible neural control mechanisms that could contribute to these changes after eccentric exercise are not yet understood.

The experiments in my thesis have aimed to provide information about these neural mechanisms, and to improve our knowledge and understanding of how the nervous system adapts to muscle damage from repeated eccentric contractions and provides protection against muscle injury from subsequent bouts of eccentric exercise. The studies described in my thesis utilised the challenging technique of directly recording motor unit activity from human elbow flexor muscles to assess for the very first time changes in the correlated discharge of action potentials (Chapter 2), and motor unit recruitment threshold forces (Chapter 3) following a single bout of eccentric exercise. Furthermore, I wanted to exam

long-lasting (≥24 hrs) changes in motor unit activity that may contribute to reduced muscle damage with repeated bouts of eccentric exercise (i.e. the "repeated bout effect"; Chapter 4).

In this introductory chapter, I will briefly describe the postulated mechanisms, indicators of muscle damage and neural adaptations to eccentric exercise, along with reviewing what is currently known about changes in motor unit activity with different tasks and exercise.

1.2. Eccentric Exercise

Muscle fibres generate tension during activation through the cycling of actin and myosin cross-bridges. During an isometric contraction, the isometric force generated is equal to the external load on the muscle, resulting in a static contraction where the length of the muscle remains the same. If the force generated by the muscle is larger than the external load on the muscle, the muscle will shorten in length. This is known as a concentric contraction, and is the result of the actin filaments sliding closer together, towards the centre of the sarcomere. On the other hand, if the isometric force generated by the muscle is insufficient to overcome the external load on the muscle, the muscle will be forcibly lengthened. This is called an eccentric contraction, and is due to the actin filaments sliding further apart from each other, away from the centre of the sarcomere.

Each of the three types of muscle contractions are used regularly during everyday activities. For example, posture when we stand or sit is maintained with isometric contractions; activities such as swimming, cycling, walking up hill and lifting objects are comprised of concentric contractions; and activities such as horse riding, skiing, downhill

walking, and lowering of an object, where our muscles perform a braking action to control the motion of the body, involve eccentric contractions.

There are several unique features of lengthening contractions, including a lower activation of the muscle during maximal eccentric contractions in comparison to isometric or concentric actions (Enoka 1996; Kellis and Baltzopoulos 1998; Westing et al. 1991), a reduced size of evoked potentials in the muscle by transcranial and peripheral nerve stimulation during eccentric exercise (Abbruzzese et al. 1994), a greater amount of force generated during an eccentric contraction than isometric force despite the net metabolic cost being considerably less (Edman et al. 1978; Webber and Kriellaars 1997), and a reduced susceptibility to fatigue during repeated eccentric actions (Tesch et al. 1990). Unlike concentric or isometric exercise, eccentric exercise is also known to produce muscle damage and soreness a day after the exercise. Hough in 1902 was the first to publish experimental evidence of delayed muscle soreness after eccentric exercise. Since this finding, subsequent studies have established that this delayed onset muscle soreness is greatest following eccentric compared with concentric exercise (Armstrong 1984; Davies and White 1981; Newham et al. 1988; Talag 1973), and is associated with the muscle damage produced by the repeated eccentric contractions.

1.2.1. Mechanisms of muscle damage

There are at least two prominent signs of muscle damage that include the presence of over-stretched and disrupted sarcomeres in myofibrils and damage to the excitation-contraction (E-C) coupling process. The initial event of muscle damage resulting from eccentric exercise remains a point of controversy with some studies taking the view that the initial muscle damage starts with the overstretching of sarcomeres (Morgan and Allen 1999;

Proske and Morgan 2001), however others view the damage process to begin with the impairment to components of the E-C coupling system (Warren et al. 2001).

The disruption to sarcomeres is thought to result from repeated eccentric contractions progressively stretching more and more sarcomeres, with the weakest sarcomeres taking up most of the stretch as they are closer to the descending limb of the sarcomere length-tension curve where most damage occurs. This process continues to be repeated, with the next-weakest sarcomere taking up the stretch, and so on (Proske and Morgan 2001). It is thought that the overstretched sarcomeres are randomly distributed along the muscle fibres. The majority of myofilaments in the overstretched sarcomeres are able to re-interdigitate and resume normal function, however some will be unable to do so and therefore become disrupted (Talbot and Morgan 1996). The number of disrupted sarcomeres is thought to increase with repeated eccentric contractions, until a point is reached where damage to the membrane of the sarcoplasmic reticulum, transverse tubules or sarcolemma occurs (Armstrong et al. 1991), resulting in an uncontrolled release of calcium into the sarcoplasm.

Impairment of the E-C coupling process has previously been declared to account for ~ 75% of the reduction in force after eccentric exercise (Warren et al. 2001). Abnormal arrangement of t-tubules following eccentric contractions may also support the hypothesis of damage to E-C coupling being the primary event (Takekura et al. 2001). Damage to t-tubules would result in the inactivation of some sarcomeres. If these inactivated sarcomeres were randomly scattered among myofibrils the sarcomere length distribution would be non-uniform and result in a shift in optimum length for peak active force, similar to the result if the primary event was sarcomere disruption. Nonetheless, although the

outcome of eccentric exercise is damage to the membrane of sarcoplasmic reticulum, transverse tubules or sarcolemma, the primary event leading to this membrane damage remains to be determined.

1.2.2. Indicators of muscle damage in humans

The extent of exercise-induced muscle damage experienced is variable in different people. This is likely due to previous training, lifestyle differences, as well as age (Jones et al. 1986). Several indicators of muscle damage are used to assess the amount of muscle damage incurred by eccentric exercise. These include delayed-onset muscle soreness, a rise of passive tension in the muscle, and a drop in force production.

Delayed-onset muscle soreness

Delayed onset muscle soreness (DOMS) begins 6-8 hrs after eccentric exercise, peaks at 48 hrs, and can last up to a week depending on the severity of the muscle damage (Jones et al. 1987). There are many simultaneous intramuscular events that occur during this period, including proteolysis (directed digestion of proteins by proteases), which can be triggered following a rise in intracellular calcium and act to assist in the breakdown of damaged fibres. An inflammatory process also begins, with products from this response acting to sensitise nociceptors (pain receptors sensitive to tissue damage) in and around the damaged tissues, resulting in muscle tenderness. Accompanying the inflammation is oedema, which most likely accounts for the muscle swelling that is also experienced (Proske and Allen 2005). The magnitude of DOMS does not necessarily reflect the amount of muscle damage present after eccentric exercise, nor is it influenced by the intensity of eccentric exercise, as are all other indirect markers of muscle damage (Nosaka and Newton 2002).

A shift of optimum length for force generation

A shift in optimum length to longer muscle lengths for peak force generation is also present following eccentric exercise. This shift has not only been observed in human muscles (Brockett et al. 2001; Chen et al. 2006; Jones et al. 1997; Philippou et al. 2004; Prasartwuth et al. 2006) but also amphibian muscle (Morgan et al. 1996; Talbot and Morgan 1998; Wood et al. 1993) and rat muscle fibres (Yeung et al. 2002). The shift to a longer muscle length is independent of fatigue (Morgan et al. 2004) and is a reliable measure correlated with the amount of muscle damage produced by the repeated eccentric contractions (Jones et al. 1997). The shift in optimum length is thought to be the result of an increase in series compliance of the fiber, due to disrupted non-contracting sarcomeres lying in series along the myofibril with still functional sarcomeres (Morgan 1990). This increase in compliance increases the resting length of the fiber, resulting in a shift in optimum muscle length for peak active force to longer muscle lengths (Jones et al. 1997).

Rise in passive tension

An increase in whole-muscle passive tension is also known to be specifically associated with muscle damage following eccentric exercise (Jones et al. 1987; Whitehead et al. 2003; Whitehead et al. 2001). However, unlike DOMS, but similar to the shift in optimum length and reduced active tension, an increase in passive tension occurs immediately after eccentric exercise and is therefore not associated with muscle swelling as was originally thought. An increase in passive tension is indicated in the human elbow flexors by a slightly more flexed elbow angle of a relaxed arm (Jones et al. 1987). One explanation for a rise in passive tension following eccentric exercise is damage and shortening of parallel, connective tissue structures (Jones et al. 1987). An alternative explanation for the rise in passive tension is the disruption of sarcomeres, leading to membrane damage and an

uncontrolled release of calcium into the sarcoplasm, which activates the contractile filaments to develop an injury contracture (Proske and Allen 2005). This active tension would be generated in the absence of any EMG.

Drop in force production

A more immediate effect of muscle damage following eccentric exercise is a reduction in active tension. This reduced force capacity is greatest immediately after the exercise and remains depressed for up to a week later (Jones et al. 1997; Whitehead et al. 1998). A reduction in force is also observed following a series of concentric contractions, but this effect only lasts 1-2 hrs (Proske and Allen 2005; Walsh et al. 2004). This suggests that both metabolic fatigue and muscle damage account for a reduction in force 1-2 hrs after eccentric exercise, but importantly it appears likely that only damage to the muscle causes the extended reduction in force. Also highly associated with eccentric exercise is low-frequency fatigue, a loss of force at low frequencies of stimulation with normal or near-normal force with high frequency tetanic stimulation. Unlike muscle fatigue that is recovered 1-2 hours after the exercise, low-frequency fatigue can take 3-4 days to recover (Jones et al. 1989) and may therefore contribute to the extended reduction in force following repeated eccentric contractions. The mechanism of low-frequency fatigue most likely involves a reduced availability of calcium from the sarcoplasmic reticulum, resulting in less calcium release per action potential, and therefore impaired E-C coupling (Jones et al. 1989; Newham et al. 1983).

1.2.3. Adaptation to eccentric exercise

It is well known that a single bout of unaccustomed eccentric exercise can provide protection against damage to skeletal muscle following a repeated bout of the same

exercise performed a few days to several months later (Chen 2003; Chen and Nosaka 2006; Clarkson et al. 1992; McHugh et al. 1999; Nosaka et al. 2001). This adaptation process, otherwise known as the "repeated bout effect", was first reported by Hough in 1902, and is characterised by reduced symptoms of muscle damage, including a faster recovery of muscle strength and less significant development of muscle soreness (Clarkson and Tremblay 1988; Golden and Dudley 1992; Mair et al. 1995; Newham et al. 1987; Nosaka et al. 1991). Although the "repeated bout effect" has been shown in many studies, consensus to the actual mechanism remains debateable but is thought to involve adaptation within both the muscle and nervous system (McHugh et al. 1999).

There are several changes in the muscle that may contribute to the adaptation of a repeated bout of eccentric exercise. As the initial bout of eccentric exercise is thought to disrupt the muscle's sarcomeres and connective tissue, strengthening of the sarcolemma and remodelling of the intermediate filaments may occur as part of the adaptation to reduce muscle damage during a repeated bout of exercise (Armstrong et al. 1991). This is supported by the finding of adaptation in the human biceps brachii muscles that was attributed to a decline in muscle mass from the removal of a small population of susceptible fibres damaged after the initial bout (Foley et al. 1999). Other studies have shown, however, that a repeated bout effect can occur when only minimal muscle damage is induced after the first bout of eccentric exercise. If there is insufficient damage of susceptible muscle fibres from the initial bout, and these fibres were therefore not completely degraded and removed, then it's possible that they would be damaged after a repeated bout of the exercise. This result, however, has not been consistently shown (Brown et al. 1997; Clarkson and Tremblay 1988; Nosaka et al. 2001; Schwane and Armstrong 1983).

An increase in the number of sarcomeres in series in the muscle fibres after the initial bout of eccentric exercise may also provide protection against a subsequent bout of eccentric exercise (Morgan 1990). It has been known since the 1970's that muscles can adapt to changes in their functional length through immobilization of the limb, at long or short lengths, by increasing or decreasing the number of sarcomeres in a muscle fibre. This has been shown by immobilizing the soleus muscles in mice at a long muscle length, resulting in a 20% increase in sarcomere number within one week, that was rapidly reversed after the immobilization ceased (Williams and Goldspink 1978). Further studies showed that the changes in sarcomere number were reflected in the muscle's length-tension relationship (Williams and Goldspink 1978). Direct evidence for the addition of sarcomeres following eccentric contractions comes from experiments where rats ran on an inclined or declined treadmill for a week (Lynn and Morgan 1994). On average, 11% more sarcomeres were found in the vastus intermedius muscles from animals that ran downhill, and the optimum angle for maximal torque production occurred at a smaller knee angle, representing a longer muscle length, compared to those that ran uphill. It has also been shown that if these rats underwent an acute series of eccentric contractions, a smaller shift in optimum knee angle was observed in the decline-trained group compared with the inclined-trained group, indicative of less muscle damage occurring. An increase in sarcomere number from immobilization has been shown to occur within 5 days. In humans, indicators of fibre regeneration have been reported as early as 72 hours after exercise-induced muscle damage, with 'normal' fibre structures reappearing 6 days after the exercise (Friden et al. 1983; Jones et al. 1986). This suggests that the addition of sarcomeres in series after an initial bout of eccentric exercise may provide protection

against muscle damage following a subsequent bout of the exercise performed one week later.

Neural mechanisms are also thought to be involved in exercise-induced muscle damage and adaptation, especially since it is well known that eccentric compared with concentric exercise requires less motor unit activation for a given level of force, as shown from EMG recordings (Bigland and Lippold 1954; Komi et al. 1987; Moritani et al. 1987). It has been proposed that a large amount of stress on a relatively small number of active fast-twitch fibres causes the initial exercise-induced muscle damage (Moritani et al. 1988). During the repeated bout of eccentric exercise, a shift to slow-twitch muscle fibre activation (Golden and Dudley 1992; Warren et al. 2000) and/or an increase in motor unit activation, such as increased motor unit synchronization, may distribute the contractile stress over a greater number of motor units, resulting in less muscle damage being produced (Nosaka and Clarkson 1995).

The majority of evidence in support of a neural adaptation to eccentric exercise-induced muscle damage comes from strength training studies. Hortobagyi et al. (1996) showed that eccentric-strength training of the knee extensors resulted in a 42% increase in eccentric contraction torque, and was associated with an increase in integrated EMG (89%). Concentric training in comparison resulted in a 36% improvement in concentric contraction torque and a 39% increase in integrated EMG. Strength improvements in eccentric torque of 30% were also shown in the unexercised contralateral muscles (Hortobagyi et al. 1996; Hortobagyi et al. 1997), further reflecting an adaptation within the nervous system after eccentric exercise. Although a link between increased neural activity and increased strength is shown by these studies, it is not shown that increased neural

activity causes a reduction in the susceptibility to muscle damage. Conflicting evidence of a neural adaptation comes from a repeated bout effect resulting from electrical stimulation of rat tibialis anterior muscles (Sacco and Jones 1992). The force measured in the eccentrically exercised muscles 3 days after the first bout was 48% of the non-exercised control muscles. After a repeated bout of the same exercise, the force measured 3 days later was 80% of the control value (Sacco and Jones 1992). It is therefore thought that the protective effect of eccentric exercise cannot be entirely attributed to neural adaptations.

More recent evidence in support of a neural adaptation comes from a 30% decrease in tibialis anterior surface EMG median frequency during a repeated bout of eccentric exercise (Warren et al. 2000). The authors interpret these data as an increase in recruitment of slow motor units and a decrease in activation of fast motor units during the repeated bout of exercise. However, there are several limitations of surface EMG recordings, including signal cancellation from the positive and negative phases of motor unit potentials overlapping, resulting in underestimation of the amount of motor unit activity (Day and Hulliger 2001; Keenan et al. 2005). A more accurate measure of motor unit activity is to use intramuscular recordings of the discharge of identifiable motor units (Merletti and Parker 2004), and I have used this technique to investigate neural adaptations to eccentric exercise in the experiments in my thesis.

1.3. Neural Adaptations to Eccentric Exercise

It is well known that eccentric exercise causes damage to the muscle, but the adjustments and adaptations within the nervous system are less well established. Changes within the nervous system have been illustrated through alterations at both the central and peripheral

level, including altered voluntary activation, reflex sensitivity, muscular co-activation, and EMG and force control.

1.3.1. Voluntary activation

The voluntary activation of a muscle has been most commonly assessed with interpolation of a stimulus to the motor nerve during a maximal voluntary contraction. If this stimulus evokes an increase in force then it is assumed that voluntary activation of the muscle is not complete. A reduction in voluntary activation of the muscle after eccentric exercise has been shown by an increase in the production of force when the motor cortex or motor nerve is stimulated, in comparison to the force produced during an MVC (Prasartwuth et al. 2005). This suggests that voluntary drive to the muscle is limited by inhibition at the motor cortex and/or the motoneurones in the first 24-hrs after eccentric exercise, and contributes to the initial loss of force after the exercise. Effects on the motor pathway for force production may include changes in either the generation of descending drive or afferent discharge. Voluntary activation by both cortical and nerve stimulation has been shown to be impaired during fatiguing isometric exercise (Gandevia et al. 1996). However, voluntary activation is impaired for the first 24-hrs after eccentric exercise (Prasartwuth et al. 2005), but muscle fatigue is only present 1-2 hours after the exercise (Walsh et al. 2004), and is therefore unlikely to be contributing to this effect. Reduced voluntary activation has also been associated with the firing of group III and IV muscle afferents (Gandevia et al. 1996). However, delayed-onset muscle soreness is not present immediately after the exercise, beginning as early as 6-8 hrs and peaking at 48 hrs after eccentric exercise. It therefore seems unlikely that muscle pain is directly related to changes in voluntary drive. Although the mechanism for reduced voluntary activation

after eccentric exercise remains to be determined, this phenomenon shows that the nervous system can adapt to repeated eccentric contractions.

1.3.2. Reflexes

Altered reflex sensitivity has been shown in several studies following exercise-induced muscle damage. A reduced soleus H-reflex was present immediately after downhill running, but not 24-hrs later (Bulbulian and Bowles 1992). Stretch-shortening cycle exercise, which involves concentric and eccentric contractions, resulted in a decrease in the amplitude of the physiological stretch reflex in the lateral gastrocnemius muscle immediately after the exercise and remained reduced until four days later (Nicol et al. 1996). Further research discovered that the H-reflex and physiological stretch reflex amplitudes in the soleus muscle were decreased for up to 10 days after the exercise (Nicol et al. 1997). There are several potential mechanisms that may contribute to this reduced reflex sensitivity after eccentric exercise. Damage to the structure of the connective tissue, skeletomotor fibres and/or muscle spindles as a result of the exercise may decrease Ia afferent discharge frequency, resulting in reduced summation of excitatory post-synaptic potentials onto the alpha motoneuron pool (Avela et al. 1999a; Avela et al. 1999b; Nicol et al. 1996). Alternatively, reduced reflex sensitivity may result from increased discharge frequency of group III and IV muscle afferents which may cause presynaptic inhibition of Ia afferent synapses with alpha motoneurons as well as increased summation of inhibitory post-synaptic potentials to the alpha motoneuron pool (Avela et al. 1999a; Avela et al. 1999b; Duchateau and Hainaut 1993; Nicol et al. 1996).

1.3.3. Muscular co-activation

An increase in antagonist muscle co-activation following eccentric exercise was first reported in the wrist flexors during an extensor torque tracking task as well as during a sustained 50% MVC (Leger and Milner 2001b). A two-fold increase in co-activation was later shown in the elbow extensors during submaximal isometric contractions of the elbow flexor muscles after eccentric exercise (Semmler et al. 2007). Such co-activation is a common occurrence when a new skill is learnt (Solomonow et al. 1988), or during maximal contraction of the agonist muscle (Carolan and Cafarelli 1992; Dimitrijevic et al. 1992; Milner et al. 1995), and may indicate an attempt to maintain joint stability (Baratta et al. 1988). Possible mechanisms include increased common drive to agonist and antagonist muscles or reduced reciprocal inhibition of the antagonist muscle when the damaged muscle is activated (De Luca 1987).

1.3.4. Electromyography and force control

Recent studies have found an association between a reduction in force following eccentric exercise and increased muscle activity (Carson et al. 2002; Hamlin and Quigley 2001; Komi and Viitasalo 1977; Leger and Milner 2001a; Prasartwuth et al. 2005; Weerakkody et al. 2003). Komi and Viitasalo (1977) were the first to report an increase in EMG activity after eccentric exercise. More recently, Weerakkody *et* al. (2003) also found a substantial increase in EMG in the biceps brachii muscle immediately after eccentric exercise, which remained elevated 24 hrs and 48 hrs after the exercise and only returned to pre-exercise levels 1 week later. Interestingly, no change in EMG was observed after concentric exercise, suggesting that the increased muscle activity was related to muscle damage from eccentric exercise, rather than muscle fatigue. This finding was confirmed in a subsequent study, where the greatest increase in EMG occurred at low forces (3-4 times

greater at 5% and 20% MVC) immediately after the exercise, which had recovered 24-hrs later (Semmler et al. 2007).

The ability to produce an intended limb position and achieve a desired force during a voluntary contraction is limited by the presence of force fluctuations (Enoka et al. 2003; Moritz et al. 2005a). An increase in force fluctuations has also been found following eccentric exercise (Lavender and Nosaka 2006; Leger and Milner 2001a; Saxton et al. 1995). Lavender & Nosaka (2006) showed increased fluctuations in force during a 30% sub-maximal elbow flexor contraction. This increase was present immediately and 1 hr after eccentric exercise and returned back to pre-exercise levels 24 hr later. Once again, these changes were not present following concentric exercise. A subsequent study showed increased fluctuations in force after eccentric exercise of the elbow flexors, especially at low force levels. Force fluctuations were 3-4 times greater at 5% MVC, and 2 times greater at 50% MVC (Semmler et al. 2007).

Several possible mechanisms have been suggested to account for an increase in elbow flexor EMG activity at low levels of activation following eccentric exercise, such as muscle co-activation, low-frequency fatigue, and motor unit synchronization. An increase in antagonist muscle co-activation would result in increased elbow flexor EMG to produce the required level of elbow flexion force, as antagonist muscle activation is increased. The presence of low-frequency fatigue (greater relative reduction in force when activated at low frequencies (Edwards et al. 1977)) after eccentric exercise would require the recruitment of new motor units along with increased discharge rate of already active motor units to overcome the loss of force-providing capacity, resulting in an increase in EMG. However, it is unknown whether motor unit activity is altered following eccentric exercise

as no studies have addressed this issue to date. This was my aim of this thesis. To examine the effect of motor unit synchronisation on EMG activity and force fluctuations, Yao *et al*., (2000) used a computer model that manipulated the relative timing of action potentials across the pool of motor neurons to generate various levels of motor unit synchronisation. High-synchrony, moderate-synchrony and no-synchrony conditions were simulated. For moderate- and high-synchrony conditions, average rectified EMG and fluctuations in force were found to be much greater than when no synchrony was present (Yao et al. 2000). These findings suggest that increased motor unit synchronisation could be one possible mechanism responsible for the increased EMG and force fluctuations observed after eccentric exercise. It remains unknown, however, if motor unit synchronization is altered after exercise-induced muscle damage. This was the first aim of my thesis and is examined in Chapter 2.

1.4. Single Motor Unit Activity

A motor unit is the unitary functional element of the neuromuscular system, and is comprised of a motor neuron in the ventral horn of the spinal cord, its axon, and all of the skeletal muscle fibres that the axon innervates. A motor neuron can innervate tens to thousands of muscle fibres, with an average of ~ 300 (Enoka and Fuglevand 2001). At a muscle's optimum length, the number of muscle fibres innervated by an individual motor neuron determines the magnitude of force that a motor unit can generate from a single action potential (Edstrom and Kugelberg 1968; Feinstein et al. 1955).

Skeletal muscle is composed of three major types of muscle fibres; slow-oxidative (type 1), fast-oxidative (type IIa), and fast-glycolytic (type IIx) (Scott et al. 2001). The three fibre types have two main differences, their speed of contractions and the pathway they

use for ATP synthesis. Motor units are also classified in a similar manner to muscle fibres, as the same fibre type is found for all the fibres in a single motor unit. Consequently, motor units are normally classified depending on physiological properties of their muscle fibres: slow (S), fast-fatigable (FF) or fast fatigue-resistant (FR).

1.4.1. Recording motor unit activity

Surface electromyography (EMG) of a muscle is recorded by adhesive electrodes placed on the skin overlying the muscle, giving a record of the action potentials generated by active motor units from within the muscle of interest (Farina et al. 2004). It is for this reason that during muscle contractions surface EMG is often used to estimate the motor output from the spinal cord. However, as a global measure of muscle activation, modest changes in motor unit activity are unable to be detected with surface EMG. The limitations of surface EMG recordings have been known for some time and are thought to include signal cancellation from the positive and negative phases of concurrently active motor unit potentials resulting in underestimation of the amount of motor unit activity (Day and Hulliger 2001; Keenan et al. 2005).

A more accurate and preferred measure of motor unit activity is to use intramuscular electrodes to record the discharge of identifiable motor units (Merletti and Parker 2004). Due to the faithful transmission of each neuronal action potential to the muscle fibers this recording technique provides valuable information on the discharge characteristics of motor neurons in the spinal cord. Several different electrodes have been developed over the years including fine-wire electrodes (Milner-Brown et al. 1973), subcutaneous electrodes (Enoka et al. 1989); concentric needle electrodes (Stalberg et al. 1996), arrays of electrodes spread over the surface of the muscle (Merletti et al. 2001), and macro-EMG

(Stalberg 1980). The most common electrode used during low-force contractions is fine-wire electrodes (Milner-Brown et al. 1973). This method consists of percutaneously inserting several fine-wire electrodes 1-2 cm deep into the muscle. Each electrode consists of insulated (except at the end), stainless-steel wires (10-50 μm diameter) threaded through the lumen of a disposable hypodermic needle. The needle is removed following insertion, leaving the wires in place in the muscle. Single motor unit action potentials are recorded via the uninsulated ends of the wires. Although the use of intramuscular electrodes is the preferred method to record single motor unit activity, it too has its limitations. Limitations include electrode movement during contraction of the muscle, only being able to accurately discriminate low threshold motor units, and the technical difficulty of recording each motor unit and the accompanied time-consuming analysis.

1.4.2. Altered motor unit activity with task/exercise

During a voluntary contraction, an increase in muscle force is associated with an increase in the EMG activity of the muscle. The force produced by a muscle depends on the number of active motor units (motor unit recruitment) as well as the rate that those units discharge action potentials (rate coding). To increase muscle force, the relative contribution of these two mechanisms varies across the working range of the muscle. Generally, at low forces, recruitment of new motor units dominates, whereas at high forces rate coding is more significant (Fuglevand et al. 1993; Moritz et al. 2005a). Once all motor units are recruited, only rate coding can increase muscle force. Recruitment and rate coding are known to play different roles in different muscles. For example, in the adductor pollicis rate coding plays a predominant role in force modulation, however motor unit recruitment has been found to dominate up to 88% of a maximal voluntary contraction as a means of force modulation in the biceps brachii (Kukulka and Clamann 1981).

Motor units are recruited based on the *size principle* (Henneman 1957), in which small motor neurons are recruited before larger motor neurons in a relatively fixed order. Although the size-based order of recruitment is quite robust, the speed and type of muscular contraction can influence the threshold force at which a human motor unit is recruited. The faster the rate of force development, the lower the motor unit recruitment threshold, as shown in the tibialis anterior muscle (Desmedt and Godaux 1977). Recruitment threshold has also been shown to be lower at short muscle lengths in comparison to long lengths during isometric contractions of the tibialis anterior muscle (Pasquet et al. 2005), and lower during dynamic contractions compared with isometric contractions of the biceps brachii muscle (Tax et al. 1989).

Along with task-related adjustments, exercise can also alter motor unit recruitment. Fatiguing exercise of the first dorsal interosseus muscle (FDI), consisting of intermittent isometric contractions at 50% MVC, was found to increase the recruitment of low-threshold (< 25% MVC) motor units (Carpentier et al. 2001). As eccentric exercise is known to produce neuromuscular fatigue, it may therefore be suggested that eccentric exercise would alter the threshold of motor unit recruitment. However, motor unit recruitment has yet to be examined following repeated eccentric contractions. This was the second aim of my thesis and is examined in Chapter 3.

The rate that a motor unit discharges action potentials and the variability of the discharge of action potentials can influence the force produced by a muscle, especially at low forces (Fuglevand et al. 1993). During voluntary contractions the minimum motor unit repetitive discharge rate is 6-10 Hz (Barry et al. 2007; Sogaard et al. 1996; Van Cutsem et al. 1997),

however, this can be higher in more proximal muscles such as the biceps brachii (Denier van der Gon et al. 1985). Unlike the threshold force of motor unit recruitment, the minimum repetitive discharge rate of motor units has been found to be relative fixed. Following 6-8 weeks of immobilization of the human adductor pollicis and first dorsal interosseous muscles, the motor unit discharge rate at recruitment was found to remain unaltered (Duchateau and Hainaut 1990). Likewise, the minimum discharge rates of single motor units in the first dorsal interosseous muscle were similar between young and old adults, suggesting that minimum motor unit discharge rate it is not affected by age (Barry et al. 2007).

When many motor units are activated, the net force produced by a muscle is not constant, but fluctuates about an average value. These fluctuations in force can be quantified by the coefficient of variation of force, and depend on the discharge and contractile characteristics of the most recently recruited motor units (Enoka et al. 2003). According to the Size Principle, small motor neurons will reach threshold before larger motor neurons (Henneman 1957). Therefore, unfused contractions of the most recently recruited (larger-force) motor units have an influence on force fluctuations, this influence being greater at low force levels where fewer motor units are activated (Graves et al. 2000). Discharge rate variability of human limb muscle motor units is typically 10-20% (Nordstrom et al. 1992; Semmler and Nordstrom 1998) and decreases when the mean discharge rate is increased (Person and Kudina 1972). Discharge rate variability has previously been shown to alter with training. Two weeks of light-load strength training (10% maximum load) involving abduction of the index finger resulted in a decrease in the coefficient of variation for discharge rate of motor units recorded from the FDI muscle during slow shortening and lengthening contractions. This was accompanied by a reduction in the

magnitude of force fluctuations during attempted constant-force contractions (Kornatz et al. 2005).

Motor unit synchronization is the tendency of motor units to near-simultaneously discharge action potentials that is greater than chance levels (Nordstrom et al. 1992). It is a measure of the common input to motor neurons during voluntary muscle contractions. For motor neurons to discharge action potentials at the same time during a voluntary contraction, the membrane potentials for action potential generation must reach threshold at similar times. This process is influenced by the concurrent delivery of synaptic input to the motor neurons and arises through either branched pre-synaptic neurones or rhythmic drive from supraspinal sources (Farmer et al. 1993a; Farmer et al. 1993b; Sears and Stagg 1976). Motor-unit synchronization is a measure of the relative contribution of correlated motor unit activity that reflects common input to motor neurons compared with independent input that the motor neurons receive. For this reason, motor-unit synchronisation gives an insight into the functional connections in the human central nervous system (CNS) during voluntary contractions. Therefore, changes in motor-unit synchronisation reflect changes in CNS strategy to perform a particular contraction (Semmler et al. 2002; Semmler et al. 2004). Motor-unit synchronization is quantified by cross-correlation of the discharge times of pairs of motor units. The size of the peak in the cross-correlation histogram reflects the relative strength of common input to the two motor neurons (Nordstrom et al. 1992). The width of the peak reflects the extent of common presynaptic input relative to separate inputs that could themselves be presynaptically synchronised. The narrower the peak, the more common presynaptic input present (Nordstrom et al. 1992; Semmler 2002).

Motor unit synchronization arises from common pre-synaptic input from branched corticospinal neurons at the level of the spinal cord (Semmler 2002). Evidence in support of this view comes from spike-triggered averaging of rectified surface EMG that suggests that single corticospinal cells in primates (monkeys) branch to facilitate approximately 75% of motor units in an intrinsic hand muscle (Mantel and Lemon 1987). This indicates that branched corticospinal inputs can contribute to motor unit synchronisation, even from within a single motor neuron pool. Other less direct observations have found that motor unit synchronisation is altered (reduced) in stroke patients following a lesion in the internal capsule (Datta et al. 1991; Farmer et al. 1993b), is absent in primary lateral sclerosis or amyotrophic lateral sclerosis patients (Schmied et al. 1999), and is present in Klippel-Feil syndrome patients between homologous hand muscles (Farmer et al. 1990). These patients are known to have abnormally branched corticospinal fibres projecting to both sides of the spinal cord. Also, the size of the central peak in the cross-correlation histogram did not alter following vigorous vibration of a hand muscle (Farmer et al. 1997), nor did it change in a patient who had a loss of sensory feedback from severe peripheral de-afferentation (Farmer et al. 1993a). This suggests that peripheral afferents are unlikely to be an important contributor to the generation of motor unit synchronisation in fresh muscle. The evidence therefore supports the view that synchronisation arises from common pre-synaptic input from branched corticospinal neurons.

Motor unit coherence is a frequency domain measure of the strength of common oscillatory input to the motor neurons that is believed to originate in cortical and sub-cortical areas, including the motor cortex (Farmer et al. 1993a; McAuley et al. 1997; Rosenberg et al. 1989). Measurements of single motor units during low-force isometric contractions of intrinsic hand muscles have previously established that motor neurons

receive common rhythmic inputs in the frequency bands 1-12 and 16-32 Hz (Farmer et al. 1993a). Several studies have shown a positive correlation between motor unit synchronization and high-frequency coherence (Farmer et al. 1993a; Halliday et al. 1999; Semmler et al. 2004), suggesting that both these features of correlated motor unit activity arise from similar mechanisms, with corticospinal inputs most likely to be involved (Datta et al. 1991; Farmer et al. 1993b). The coherence spectrum has been shown to differ for different muscles. For example, a large amplitude, low-frequency oscillation that peaks at 1-2 Hz, with minimal coherence at high frequencies has been shown in biceps brachii motor units, which is in contrast to the coherence spectrum in hand muscles (Farmer et al. 1993a; Kim et al. 2001). As well as a large amplitude, low-frequency oscillation there is also a large amount of coherence at high frequencies in the FDI. These results suggest that the relative contribution of the oscillatory inputs at low and high frequencies is different in hand and arm muscles, supporting the observations of a reduced corticospinal projection to proximal compared with distal muscles (Clough et al. 1968; Phillips and Porter 1964). It remains unknown whether eccentric exercise affects motor unit coherence and this was therefore examined in this thesis (Chapter 2).

The correlated discharge of motor units is not a fixed property of the CNS (Adams et al. 1989) having been shown to alter during different types of movement and after exercise. Motor unit synchronization is greater during extension of the FDI muscle compared with abduction (Bremner et al. 1991), as well as being greater during slow lengthening contractions of the FDI muscle compared with shortening and postural contractions (Semmler et al. 2002). It is a widely accepted view that, along with changes in cortical and spinal excitability, fatigue is associated with an increase in motor unit synchronization (Gandevia 2001). However, this view is based on computer simulations (Kleine et al.

2001; Yao et al. 2000) or experimental studies using indirect assessments from the surface EMG (Farina et al. 2002), which are likely to be misleading (Farina et al. 2004). Motor unit synchronization and coherence have been shown to not be influenced by short-term (4-8 weeks) strength training in the hand muscle (Kidgell et al. 2006) and the coherence of motor units is reduced during shortening (concentric) contractions of the wrist (Kakuda et al. 1999) and hand muscles (Semmler et al. 2002) compared with lengthening (eccentric) contractions.

Motor unit recordings have not previously been made after eccentric exercise, so it remains unknown whether muscle damage resulting from repeated eccentric contractions can alter motor unit activity and influence neuromuscular function during voluntary contractions. I will therefore examine for the first time following eccentric muscle damage changes in motor unit synchronization and coherence (Chapter 2), motor unit recruitment and discharge patterns (Chapter 3), as well as changes in motor unit activity after repeated bouts of eccentric exercise (Chapter 4). These studies have important implications for improving our knowledge and understanding of how the nervous system adapts to muscle damage from repeated eccentric contractions.

1.5. Aims and Objectives of Thesis

This thesis will focus on increasing the understanding and knowledge of the neuromuscular effects of eccentric exercise. More specifically, the aims and objectives of this thesis are:

1. To determine the effect of exercise-induced muscle damage on time- (motor unit synchronization) and frequency-domain (motor unit coherence) measures of correlated motor unit discharge during isometric contractions of biceps brachii (Chapter 2).

2. To compare changes in motor unit recruitment threshold and the minimum tonic discharge rate of motor units after eccentric exercise of elbow flexor muscles (Chapter 3).

3. To examine changes in correlated mootr unit activity and recruitment threshold forces of low-threshold biceps brachii motor units after an initial (bout 1) and repeated (bout 2) session of eccentric exercise (Chapter 4).

CHAPTER II

MOTOR UNIT SYNCHRONIZATION IS INCREASED IN BICEPS BRACHII AFTER EXERCISE-INDUCED DAMAGE TO ELBOW FLEXOR MUSCLES

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NOTE:
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2. Motor unit synchronisation is increased in biceps brachii after exercise-induced damage to elbow flexor muscles.

Dartnall, T.J., Nordstrom, M.A. & Semmler, J.G. (2008) Motor unit synchronization is increased in biceps brachii after exercise-induced damage to elbow flexor muscles *Journal of Neurophysiology, v. 99(2), pp. 1008-1019.*

CHAPTER III

ECCENTRIC MUSLCE DAMAGE HAS VARIABLE EFFECTS ON MOTOR UNIT RECRUITMENT THRESHOLDS AND DISCHARGE PATTERNS IN ELBOW FLEXOR MUSCLES

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3. Eccentric muscle damage has variable effects on motor unit recruitment thresholds and discharge patterns in elbow flexor muscles

Dartnall, T.J., Rogasch, N.C., Nordstrom, M.A. & Semmler, J.G. (2009) Eccentric muscle damage has variable effects on motor unit recruitment thresholds and discharge patterns in elbow flexor muscles.
Journal of Neurophysiology, v. 102(1), pp. 413-423.

CHAPTER IV

ADAPTATIONS IN HUMAN MOTOR UNIT ACTIVITY AFTER REPEATED BOUTS OF ECCENTRIC EXERCISE IN ELBOW FLEXOR MUSCLES.

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5. General Discussion

Over the last several decades there has been increasing interest in examining the effects of eccentric exercise. The majority of studies to date have focussed on structural changes in the muscle, as eccentric exercise is known to produce significant muscle damage, which results in numerous changes in muscle structure and function (Proske and Allen 2005). However, little is known about how the nervous system responds to repeated eccentric contractions that induce muscle damage. What is known is that eccentric exercise causes a reduction in voluntary activation (Prasartwuth et al. 2005), altered reflex sensitivity (Bulbulian and Bowles 1992; Nicol et al. 1996), increased low-frequency fatigue (Dundon et al. 2008; Jones et al. 1989; Newham et al. 1983), increased antagonist muscle co-activation (Leger and Milner 2001b), along with increased sub-maximal EMG activity (Carson et al. 2002; Hamlin and Quigley 2001; Leger and Milner 2001a; Prasartwuth et al. 2005; Semmler et al. 2007; Weerakkody et al. 2003) and more variable force control (Lavender and Nosaka 2007; Leger and Milner 2001a; Saxton et al. 1995; Semmler et al. 2007). Although these studies illustrate changes in the nervous system following eccentric exercise, no studies have examined changes at the level of single motor unit activity, which provides specific information about the activity of spinal motor neurons that can reveal details of the nature of the neural adaptations to eccentric exercise. It is possible that the series of physiological and mechanical events leading to muscle damage from eccentric exercise may act to influence the neural inputs responsible for correlated motor unit discharge and the threshold force at which motor units are recruited. It was hypothesized that eccentric exercise would result in increased motor unit synchronization (Chapter 2) and a reduction in the force at which motor units are recruited (Chapter 3) immediately after the first bout of eccentric exercise.

It is well known that a single bout of eccentric exercise can provide protection against damage to skeletal muscle following a repeated bout of eccentric exercise performed a few days to several months later. One potential mechanism for the "repeated bout effect" is a change in motor unit activity during the second bout of eccentric exercise. For this mechanism to be effective, the initial bout of exercise must produce long-lasting changes in motor unit activity that is evident before or during the repeated bout of eccentric exercise. To provide evidence on this point I have examined the adjustments in single motor unit activity after a single (Chapters 2 and 3) and repeated bout (Chapter 4) of eccentric exercise in elbow flexor muscles.

5.1. Summary of findings

Muscle damage was induced in the present experiments by controlled lowering of a hand-held load, set at 40% of the subject's isometric MVC at 90° flexion, requiring eccentric contraction of the elbow flexor muscles (Chapter 2 and 3), or with maximal voluntary eccentric contractions of the elbow flexors on an isokinetic dynamometer (Chapter 4), to induce a ~ 40% reduction in MVC force in all subjects. Along with a lasting reduction in MVC force, I found a reduction in relaxed elbow joint angle (indicative of a rise in passive tension) up to 24-hrs after the exercise and the presence of delayed-onset muscle soreness a day later, consistent with results from previous studies. Also confirming results from other studies I found an increase in sub-maximal biceps brachii EMG activity and increased force fluctuations for up to 24-hrs after the exercise, as well as increased antagonist activity from triceps brachii EMG immediately after eccentric exercise.

Following a single bout of eccentric exercise, I found an increase in correlated motor unit activity (motor unit synchronization and coherence; Chapter 2) and a reduction in the force

at which motor units were recruited (Chapter 3) that lasted for at least 24 hours after the exercise. Minimum motor unit discharge rates were also influenced by eccentric exercise, but this recovered 24 hours later (Chapter 3). These findings are the first recordings from single motor units in any muscle to examine correlated motor unit activity and recruitment threshold forces after exercise-induced muscle damage, and showed that the series of physiological and mechanical events leading to muscle damage from eccentric exercise alters the correlated discharge behavior and recruitment threshold of human motor units in elbow flexor muscles for at least 2 days. From these findings, and some evidence of a potential neural adaptation contributing to the "repeated bout effect", I hypothesised that a lasting adaptation in correlated motor unit activity and/or motor unit recruitment may contribute to the "repeated bout effect", which results in reduced muscle damage from a subsequent bout of eccentric exercise. This was examined in Chapter 4.

In the experiments described in Chapter 4, a subsequent bout of maximal isokinetic eccentric exercise performed 7 days after the initial bout of eccentric exercise resulted in reduced symptoms of muscle damage, such as a faster recovery of muscle strength, and less significant development of muscle soreness. Motor unit activity measured 7 days after the initial bout of exercise (and immediately before the repeated bout) showed elevated motor unit synchronization, but a recovery of motor unit recruitment threshold to pre-exercise levels. These findings are the first to demonstrate a long-lasting increase in motor unit synchronization following an unaccustomed bout of eccentric exercise, representing a long-term neural adaptation. This result suggests a potential role for motor unit synchronization in reducing muscle damage after a repeated bout of eccentric exercise, possibly by distributing the applied external load over a greater number of motor units during lengthening contractions in the damaged muscle.

5.2. Implications and future directions

Eccentric contractions are a common occurrence in everyday activities and in most sporting activities such as, jumping, running, throwing and weightlifting. There are several unique features of lengthening contractions, including a lower activation of the muscle during maximal eccentric contractions in comparison to isometric or concentric actions, a reduced size of evoked potentials in the muscle by transcranial and peripheral nerve stimulation during eccentric exercise, a greater amount of force generated during an eccentric contraction than isometric force despite the net metabolic cost being considerably less, an altered order of motor unit recruitment during sub-maximal eccentric contractions, and a reduced susceptibility to fatigue during repeated eccentric actions. This suggests that lengthening contractions require a unique activation strategy by the nervous system, thereby potentially maximizing the activity and protecting the health of high-threshold motor units. The use of these high-threshold motor units is minimal during everyday activities, but is essential for the performance of intense athletic sports and for emergency movements that require a high level of force from the muscle in a short time-frame. However, there are also adverse consequences of eccentric contractions, including the production of muscle damage. Muscle damage is a result of overstretched and disrupted sarcomeres, causing sarcolemmal membrane damage and an uncontrolled release of calcium (see Proske and Allen 205), ultimately leading to impaired muscle function.

The studies reported here provide the first recordings of single motor unit activity after eccentric muscle damage in humans. These findings have important implications for improving our knowledge and understanding of how the nervous system adapts to muscle damage from repeated eccentric contractions, and how these adaptations of spinal motor

neurons may provide protection against muscle injury following subsequent bouts of eccentric exercise.

The results from my thesis have provided the first evidence of a long-lasting increase in motor unit synchronization that persists for at least 7 days until a repeated bout of the same exercise is performed. However, a direct link between increased motor unit synchronization and reduced muscle damage remains to be examined. There remain several other plausible mechanisms to explain the "repeated bout effect" including structural and bio-chemical changes in the muscle, although consensus to the actual mechanism is yet to be determined. It would therefore be of interest in future studies to induce an increase in motor unit synchrony, without the associated structural and chemical changes experienced with exercise-induced muscle damage. By inducing these changes before a bout of eccentric exercise we can therefore examine direct effect of motor unit synchronization on exercise-induced muscle damage.

Factors that have been shown to increase motor unit synchronization and could therefore be used in these studies include exercise, as well as the injection of a drug. For example, motor unit synchrony, estimated from the surface EMG, was shown to increase following a 6-week strength training program of the first dorsal interosseus (FDI) muscle in untrained participants (Milner-Brown et al. 1975). A similar finding was observed when the effect of habitual physical activity on motor unit synchronization was examined using the cross-correlation of motor unit discharge in highly skilled musicians, strength trained weightlifters and untrained individuals (Semmler and Nordstrom 1998). During a simple finger abduction task the strength of motor unit synchronization was found to be greatest for the dominant and non-dominant hands in weightlifters compared with musicians and

untrained individuals. However, a more recent study found no change in motor unit synchrony following short-term strength training of the FDI (Kidgell et al. 2006). This suggests an important implication of the results from Chapter 2 which demonstrate an increase in motor unit synchronization after eccentric exercise. The muscle damage component resulting from the eccentric contractions could therefore provide the stimulus for increasing motor unit synchrony with training. An increase in motor unit synchronization can also be induced by pharmacological means. It has previously been shown that a short-lasting injection of L-acetylcarnitine (L-Ac) causes an increase in motor unit synchrony by inducing a reversible increase in recurrent inhibition (Mattei et al. 2003). It may therefore be possible to inject L-Ac before a bout of eccentric exercise to examine the effect increased motor unit synchronization has on reducing the effect of muscle damage produced by repeated eccentric contractions.

Neural factors associated with muscle damage along with adaptations to eccentric exercise in specific populations of subjects, such as older adults (60-85 years old), could also be examined in future studies. It is known that advancing age results in changes to the nervous system, including a considerable loss of cortical (Henderson et al. 1980) and spinal motor neurons (Doherty et al. 1993), resulting in a decrease in the excitability of the corticospinal pathway (Eisen et al. 1991; Sale and Semmler 2005). It would therefore be worth examining whether the extent of muscle damage is different in an older population of subjects. If such a difference is found we could then examine whether the nervous system contributes to these differences.

These future studies will aid in improving our knowledge and understanding of how neural adaptations to eccentric exercise can protect against muscle damage when eccentric

exercise is performed. By improving our understanding of this topic more effective ways of reducing muscle damage following repeated eccentric contractions, which are a common occurrence in everyday activities and in athletic competition, can be determined. A greater understanding of the neural mechanisms responsible for acute adjustments and chronic adaptations to eccentric exercise is necessary for refining interventions for injury prevention, injury treatment, and strength training.

6. Appendices

6.1. Appendix I: Publications arising from this thesis.

Dartnall, T.J., Nordstrom, M.A., & Semmler, J.G. (2008) Motor Unit Synchronization is Increased in Biceps Brachii after Exercise-Induced Damage to Elbow Flexor Muscles. *Journal of Neurophysiology* 99: 1008-1019.

Dartnall, T.J., Rogasch, N.C., Nordstrom, M.A., & Semmler, J.G. (2009) Eccentric Muscle Damage Has Variable Effects on Motor Unit Recruitment Thresholds and Discharge Patterns in Elbow Flexor Muscles. *Journal of Neurophysiology* 102: 413-423.

Dartnall, T.J., Nordstrom, M.A., & Semmler, J.G. Adaptations in human motor unit activity after repeated bouts of eccentric exercise in elbow flexor muscles. To be submitted to *Journal of Neurophysiology*.

6.2. Appendix II: Presentations and abstracts arising from this thesis.

Dartnall, T.J. (2006) Neuromuscular Effects of Eccentric Exercise. Discipline of Physiology Seminar Series, University of Adelaide, Australia.

Dartnall, T.J. (2007) Motor Unit Synchronization is Enhanced Following Eccentric Exercise of the Elbow Flexor Muscles. Research Centre for Human Movement Control, Motor Control Seminar Series, University of Adelaide, Australia.

Dartnall, T.J., Nordstrom, M.A., & Semmler, J.G. (2007) Motor Unit Synchronization is Increased in Biceps Brachii after Exercise-Induced Damage to Elbow Flexor Muscles. IBRO World Congress of Neuroscience Satellite Meeting, Darwin, Australia.

Dartnall, T.J., Rogasch, N.C., Nordstrom, M.A., & Semmler, J.G. (2008) Increased Motor Unit Recruitment and Minimum Discharge Rates After Exercise-Induced Damage to Elbow Flexor Muscles. Society for Neuroscience Meeting, Washington, DC.

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