Strength training for partially paralysed muscles in people with spinal cord injury

This thesis is submitted in satisfaction of the requirement for the degree of Doctor of Philosophy

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Candidate’s declaration

I, Elizabeth Bye, declare that the work within this thesis is entirely my own and contains no material previously published or written by another person except where acknowledged in the text. I certify that this thesis has not been submitted for a higher degree to any other university or institution.

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Candidate’s Statement of Contribution to Jointly Published Work

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For this publication, I contributed to: conceptualising the research question, writing up the protocol and report, screening potentially eligible participants, conducting the research, organising the data for analysis, interpreting the results, writing the manuscript and critical appraisal of content and response to reviewers.

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As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

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Abstract

The focus of this thesis is on strengthening of partially paralysed muscles following a spinal cord injury (SCI) with a particular emphasis on the effectiveness of different interventions. Weakness, as a result of partial paralysis is the most common and debilitating secondary impairment following a SCI. Therefore, physiotherapists spend a lot of time directing their interventions at increasing strength. The focus of this thesis is to further understand the effectiveness of these interventions and the mechanisms at play responsible for strength gains. This thesis includes four projects namely a randomised controlled trial (RCT), two pretest-posttest studies and a clinimetrics study.

The first project was a multi-centred, within-participant, assessor blinded RCT which investigated the effectiveness of progressive resistance training (PRT) for increasing the strength of partially paralysed muscles following a SCI. Thirty participants were recruited from 5 spinal injury units (4 in Australia and 1 in India). We chose one partially paralysed muscle that had Grade 3 or 4 strength on Manual muscle testing (MMT) to train. Participants acted as their own controls, meaning their left or right limbs were randomly allocated to strength training while the other side received usual care only. Progressive resistance training was provided 3 times a week over a 12-week period and involved 4 sets of 10 contractions per session. The mean between-group difference for strength (primary outcome measure) at 12 weeks was 4.3Nm (95% CI, 1.9 to 6.8; favoring the intervention group). This is the first trial to demonstrate that partially paralysed muscles following SCI respond to PRT.

The second project was a pretest-posttest study, which investigated the mechanisms by which PRT increases strength of partially paralysed muscles in people with SCI. Ten community
dwelling individuals with partial paralysis (defined as Grade 1 to 4 on a 6-point MMT) of either the elbow flexor, elbow extensor, knee flexor or knee extensor muscles were recruited. The participants underwent a magnetic resonance imaging (MRI) scan prior to commencing a 6-week strength-training program followed by a repeat MRI after the last training session. The outcome of primary interest was muscle physiological cross sectional area (PCSA) measured using MRI and diffusion tensor imaging (DTI). Secondary outcome measures were isometric muscle strength measured using an isokinetic dynamometer, muscle strength measured using a 13-point MMT and mean fascicle length, muscle volume and pennation angle. The mean increase in maximal isometric strength measured using the Humac isokinetic dynamometer was 14% (95% CI, -3% to 30%) and 1.5 points (95% CI, 0.5 – 2.5) on the 13-point MMT. These results indicate no evidence of a change in muscle architecture. This suggests strength gains are due to increased neural drive or an increase in specific muscle tension.

The third project used MRI data obtained from my second project and from a cohort of able-bodied individuals to compare intramuscular fat (IMF) in neurologically intact muscles and partially paralysed muscles. The purpose of this study was to compare the fat content of partially paralysed muscles to the muscles of able-bodied individuals. I also wanted to determine the effects of a brief strength-training program on IMF in both able-bodied individuals (i.e., people without SCI) and people with partially paralysed muscles after SCI. Participants with SCI had a median of 14% (IQR 12 to 22%) IMF while able-bodied individuals had a median of 8% (IQR 6 to 10%) IMF. The mean (95% CI) increase in maximal isometric strength with training for the participants with and without SCI were 14% (95% CI, -3% to 30%) and 12% (95% CI, 4% to 20%) respectively. There was no change in IMF within the trained muscle after the strength training, either in the partially paralysed muscles of people with SCI or the muscles of the able-bodied individuals.
The fourth project was a clinimetric study to determine the inter-rater reliability of the 13-point Manual Muscle test (MMT). Weakness is one of the most common impairments following SCI. We therefore need reliable and appropriate measurement tools to use in clinical trials in which the aim is to determine the effectiveness of interventions targeting strength. Manual muscle testing is quick and easy to administer, and does not require specialised or expensive equipment such as an isokinetic dynamometer. This means it is a simple way to measure strength in multi-centred clinical trials in which access to isokinetic dynamometers is not always possible. Therefore, I felt it was important to establish the reliability of the 13-point MMT to use in clinical trials. Sixty people with complete or incomplete SCI were recruited from three spinal injury units in Sydney, Australia. Muscle strength of the wrist extensors and/or elbow flexors of the left or right side of each participant was assessed by two experienced physiotherapists on the same day. Strength was measured using the 13-point MMT using a standardised procedure. The weighted kappa coefficient (95% CI) reflecting the agreement between the two strength assessments by the two different assessors for the wrist extensors and elbow flexors were 0.96 (0.93 to 0.99) and 0.94 (0.89 to 0.99), respectively. Repeat measurements by different physiotherapists were within 1 of 13 points of each other 82% of the time for wrist extensors and 87% of the time for elbow flexors. The 13-point MMT has excellent reliability and is a simple and quick tool, which could be useful in clinical trials as an outcome measure.

This thesis set out to understand the effectiveness of strength training in partially paralysed muscles, the mechanisms behind these increases in strength, the effect of training and SCI on intramuscular fat and the reliability of a commonly used strength assessment tool. The findings of Project One and Two indicate that partially paralysed muscles do respond to strength
training, however the underlying mechanisms behind these strength gains are not clear.

Project Three indicated that strength training does not reduce IMF. This is in contrast to some studies in the able-bodied population. Lastly, MMT may be an appropriate strength assessment tool for assessing strength in clinical trials.
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Preface

This thesis contains chapters, which are intended to be read independently. Chapters 2, 3, 4, 5 contain the four projects that have been either published or submitted for publication in peer-reviewed journals. These studies are presented in the format in which they were/will be published.

- Chapter 2 is published as:
  

- Chapter 3 is published as:
  

- Chapter 4 (draft manuscript):
  
  **Bye E, Eguchi J, Harvey L, Glinsky J, Bolsterlee B, Thom J, Herbert R Intramuscular fat in people with spinal cord injury and able-bodied individuals before and after strength training.**

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Chapter 1 – Background: weakness, paralysis and strengthening interventions following SCI

Overview

The purpose of this section is to provide an outline of what will be covered in this chapter and thesis. This first chapter will outline some of the important ideas related to strengthening partially paralysed muscles in people with SCI. First, I will outline the various types of SCI and the implications and different types of weakness following SCI. I will then address the current literature about strength training in the able-bodied population explaining the key training principles. An understanding of the strength training principles in a non-paralysed muscle may provide some insight into how to strengthen partially paralysed muscles.

Part of this chapter will be devoted to what is currently known about the effectiveness of strength training in the SCI population. Due to the lack of evidence in the area we often assume that what is effective in a non-paralysed muscle is equally effective in a partially paralysed muscle. This assumption is based on the observation that following SCI, people get stronger. There are a number of cohort studies that document these changes and lead people to associate these strength gains with rehabilitation interventions. I will summarise these findings and outline the limitations of drawing conclusions from this type of study design.

The final part of this chapter addresses outcome measures. It is important that we have reliable outcome measures to quantify a person’s strength following SCI. I will outline the different ways to measure strength and the limitations of each method. I will then outline the current literature examining the effects of resistance training following a SCI as well as the
effects on other neurological populations. I will also outline the proposed mechanisms that limit force production and explain the effects of intramuscular fat on muscle function.

**Classification of SCI**

Spinal cord injuries are classified by The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). These standards were initially developed by the American Spinal Injury Association (ASIA) and later endorsed by the International Spinal Cord Society (ISCoS) (1). There are five ASIA Impairment scale (AIS) grades: namely AIS A (complete), AIS B (sensory incomplete), AIS C (motor incomplete), AIS D (motor incomplete) and AIS E (no neurological loss) (2). The distinction between complete and incomplete is solely based on the presence of S4-5 motor or sensory function. The ISNCSCI also defines a neurological level, two motor levels and two sensory levels. The neurological level is defined as the most caudal level at which sensory and motor function are intact. The sensory level refers to the most caudal, intact dermatome for both light touch and pin prick sensation. There is a sensory level for both the right and left sides. The motor level refers to the most caudal myotome with a key muscle function of at least grade 3, provided all key muscles above that level are grade 5 (3).

Spinal cord injury results in either tetraplegia or paraplegia. Tetraplegia refers to neurological damage in the cervical region of the spinal cord and results in loss of motor and/or sensory function in the upper limbs, lower limbs, trunk and pelvic organs (4). Over half of all SCI results in tetraplegia (5, 6). The remaining injuries result in paraplegia which refers to neurological damage in the thoracic, lumbar or sacral regions of the spinal cord and results in loss of motor and/or sensory function in the trunk, legs and pelvic region (7). These injuries occur in equal proportions in the three regions of the spine (thoracic, lumbar and sacral) (5, 6).
Different types of weakness

There are two types of weakness that can occur following SCI: neurologically induced weakness and non-neurologically induced weakness. Neurologically induced weakness occurs as a direct consequence of the neurological insult. This type of weakness occurs at and below the level of injury. Neurologically induced weakness is due to damage of either the upper or lower motor neurons within the spinal cord. This limits or prevents the relay of action potentials to the motor unit (8). This may result in either complete paralysis or partial paralysis.

The second type of weakness is non-neurologically induced weakness often termed deconditioning which develops as a result of disuse during periods of inactivity. This inactivity and subsequent disuse can occur acutely after injury and can be life-long depending on levels of activity. Following a SCI, a person is most likely to spend prolonged periods on bed rest while they are medically unstable. This prolonged period of inactivity results in a loss of muscle mass (9) which leads to weakness. During this acute period the person may also require mechanical ventilation typically under the effects of sedation. It is thought that sedatives may compound muscle wasting and may have a larger effect on muscle atrophy and weakness than when patients are ventilated but not sedated (10-12).

Even after the acute phase of injury, non-neurological weakness can remain a problem as individuals with SCI have among the greatest levels of inactivity compared to other populations (13). Many disuse models have been used to study the effects of inactivity, for example immobilising people in casts, lower limb suspension and bed rest (14-19). The most detrimental consequence of disuse is atrophy, which has been shown to occur at a very rapid rate. One study examined the effects of one week of strict bed rest in 10 able-bodied young
males and showed quadriceps cross-sectional area (CSA) reduced by $3.2 \pm 0.9\%$ (SEM(20)). Another study used a longer period of bed rest subjecting seven men to 6 weeks of bed rest and found a decrease in quadriceps CSA of $14 \pm 4\%$ (SD) (21). Neurological weakness may also occur together with deconditioning leading to added weakness.

Whilst there are two types of weakness that can develop following SCI my projects focused on studying the effects of strength training on neurologically induced weakness only.

**Implication of weakness and paralysis on function**

Motor impairment following a SCI can be due to paralysis, partial paralysis or non-neurological weakness (22). The extent and pattern of motor impairment largely determines a person’s functional status following SCI. Partial paralysis is caused by disruption to some but not all the motor pathways to a muscle. Paralysis occurs due to a complete disruption to the descending motor pathways (8). The implications of these impairments vary depending on the severity of injury. Not surprisingly, weakness and paralysis often have deleterious implications on quality of life and community participation (23).

People with complete tetraplegia, with lower limb paralysis and no zones of partial preservation will only have use of their upper limbs and no trunk control. The consequence of this will be a life in a wheelchair. The amount of partial paralysis to their upper limbs will vary depending on their injury level and severity. Typically, people with a neurological level of C1-C3 will have head movement with complete paralysis of their upper limb muscles; consequently they will be dependent on a chin-controlled power wheelchair. However, if a person’s injury level is lower down at C5, they will have reasonable strength in the deltoids and biceps allowing them to carry out functional activities by bringing the hand to the mouth.
These examples highlight the implications complete paralysis has on a person's overall function. In these examples paralysis is the most obvious impairment impacting on the person’s daily functional tasks.

Non-neurological weakness can also affect a person’s functional status. For example, a person with complete paraplegia, with lower limb paralysis and no zones of partial preservation, will have full innervation of their upper limb muscles. However, the strength in their upper limbs may be inadequate to sustain the demands of propelling their wheelchair up slopes or transferring in and out of their wheelchairs. Therefore, strengthening these neurologically intact muscles is important, as it will directly impact on their function.

Similarly, the strength in partially paralysed muscles has important functional implications with even small increases in strength having profound implications on function. For example, the difference between a grade 3 and grade 4 knee extensor strength in people with incomplete paraplegia may discriminate if they can walk aided versus unaided. Evidently, small changes in strength, whether that is in neurally intact muscles or partially paralysed muscles, can have a large impact on a person’s overall function and in turn their quality of life (24).

**Other implications of weakness**

Weakness not only affects a person’s overall function but it can have many other implications. These implications can impact on a person’s health, well-being, activity participation and quality of life (25, 26).
**Cardiovascular**: Weakness can diminish a person's exercise capacity (27). Exercise capacity is largely determined by active muscle mass, which drives oxygen extraction and venous return both of which are reduced in the face of extensive paralysis (28). Extensive paralysis also leads to impaired circulation below the level of injury causing blood pooling in the lower limbs, producing a decreased venous return and reduced ability to increase stroke volume of the heart (29, 30).

Most people with SCI live profoundly sedentary lifestyles due to extensive paralysis. This increases their risk of adverse health outcomes. In particular, people with SCI have a poorer cardiovascular risk profile than able-bodied individuals. This can be explained by a greater body mass index (BMI) and percentage fat mass, as well as lower total daily energy expenditure (31). A markedly reduced exercise capacity increases the risk of cardiovascular disease (32).

**Muscle atrophy**: Extensive weakness is also a problem because it is associated with muscle atrophy (33). Atrophy is not only aesthetically undesirable but can also contribute to the development of pressure ulcers (34). Without adequate padding around bony prominences such as ischial tuberosities or femoral heads, people are placed at increased risk of developing pressure ulcers. Pressure ulcers are common in people with SCI because of their impaired motor and sensory function, which limits their ability to detect pain and discomfort and move (35). They can lead to physical, psychosocial and financial consequences. In addition, they can affect a person's family and social life (36).

The other consequence of atrophy is that atrophied skeletal muscles contain accumulations of intramuscular fat (37, 38). Changes in body composition can impair a person's glucose
tolerance, insulin resistance and ultimately lead to type 2 diabetes mellitus (DM) and other metabolic disorders (38, 39).

**Contracture:** Contracture is a common complication following SCI (40, 41). It can be caused by immobility of a joint secondary to weakness (42). This is thought to cause stiffening of intra-articular structures or changes in the passive mechanical properties of muscle-tendon units (43-45). This places the joint in a shortened position and can lead to further immobility and disuse.

The implications of contracture can be detrimental to a person's overall function (46-49), for example a flexion contracture of the fingers may limit a person's ability to open the hand and grasp objects. Similarly, a plantarflexion contracture, will lead to difficulties with placing the heel to the ground throughout gait, which may lead to a fall.

Contractures not only affect a person's function but they may also lead to pain and deformity (40, 50, 51). Deformity can be aesthetically undesirable and also prevent personal hygiene for example if the fingers are contracted into a fist it will be very difficult to clean the skin of the palm of the hand. It is also thought that contractures may predispose people to pressure ulcers and sleep disturbances (52).

**Strength gains following SCI**

It is widely believed by clinicians that strength training is effective for partially paralysed muscles. However, when we examine the evidence that supports these claims they are predominantly based on clinical observation, case series and cohort studies that demonstrate increases in strength in people with SCI (24, 53-56). It is clear from these studies that recovery
of muscle strength continues for a significant period after injury. One cohort study by Ditunno assessed the upper limb motor recovery of 167 individuals with acute traumatic complete or incomplete tetraplegia (57). The participants were assessed using MMT at admission, 72 hours, 1, 2 and 3 weeks and 1, 2, 3, 6, 12, 18 and 24 months post injury. Recovery was defined as a change from less than grade 2/5 strength to a grade of 3/5 or greater strength. The results demonstrated recovery of: (i) the biceps for people with C4 tetraplegia in 70% of complete compared to 90% of incomplete injuries, (ii) the extensor carpi radialis in people with C5 tetraplegia in 75% of complete and 90% of incomplete injuries, and (iii) the triceps in people with C6 tetraplegia in 85% of complete and 90% of incomplete injuries. This study demonstrated that people with complete and incomplete tetraplegia get stronger, however it is unclear if these strength gains can be solely attributed to physiotherapy interventions as opposed to natural recovery.

There are also large cohort studies recording valuable information about natural progression of strength. The broad findings from these studies are; a third of people following SCI will experience improvements in their AIS grade, most people by one AIS grade and a lesser number by 2 or 3 grades (58). It is also common for the level of lesion to descend in patients with complete tetraplegia. In regard to the time of recovery, approximately the first 2 months following injury are the crucial months for this, however, some recovery can continue one year after injury (58, 59). These data all demonstrate that most people do become stronger following their initial injuries. The unanswered question is how much, if any, of these increases in strength can be attributed to physiotherapy or other rehabilitation interventions.

It is very difficult to answer questions about the causal link between physiotherapy (or other rehabilitation interventions) and strength from cohort studies because of the problems of
confounding. Instead, a randomised controlled trial is more appropriate. Randomised controlled trials can offer high-quality evidence about the effectiveness or ineffectiveness of interventions (60). The key feature to this study design is randomisation, which ensures that the two groups are equivalent for all known and unknown prognostic factors (61). In order to minimise bias there are several other design features of randomised controlled trials. These features can be assessed using the PEDro scale (62). The scale items include specification of eligibility criteria; random allocation to groups; concealed allocation; groups similar at baseline; blinding of subjects, therapists and assessors; outcome measures obtained from greater than 85% of subjects; intention-to-treat analysis; between-group statistical comparisons; reporting of point measures and measures of variability. Perhaps the most important feature out of all of these is blinding. Due to the nature of rehabilitation trials it is often impossible to blind patients and therapists. It is possible to blind assessors which is important as it decreases the chance of biased results that may occur when a person has a preconception about the effectiveness of the intervention. Studies with non-blinded assessors and low methodological quality tend to overestimate the size of the treatment effects (63-65).

**Strengthening interventions**

**Difference between voluntary and stimulated strength**

A key purpose of physiotherapy programs following SCI is to increase voluntary strength. The brain drives voluntary muscle contractions via the descending motor pathways. To strengthen a muscle’s voluntary capacity requires changes to peripheral and central factors. These central and peripheral factors will be discussed in further detail in later paragraphs.

Neuromuscular electrical stimulation (NMES) can be used to produce muscle force in paralysed and partially paralysed muscle. Stimulated force is produced by applying electric
current via electrodes placed on the skin, which stimulates nerves and muscles fibres. Physiotherapists typically administer electrical stimulation via surface electrodes. Electrical stimulation can be combined with resistance training and has been shown to induce hypertrophy (66-70). One study showed increases in muscle mass of up to 39% (SD +/-27%) (68) after 16 weeks of electrically-induced resistance training; other studies have shown similar results (69, 71). All studies included participants with motor complete injuries and did not report whether the lower limb muscles were partially or completely paralysed. It is important to note there are several limitations to these studies. Firstly they all have small sample sizes of between 1-14 participants meaning there is large variability in the data and the precision of the estimate is imprecise. Secondly, all except one study (69) was a pre-post test study. The lack of a control group can cause estimates of the treatment effect to be confounded by factors other than the intervention (72). Nonetheless, these studies do suggest that it may be possible to induce hypertrophy with the right training stimulus. However, the focus of this chapter and thesis is on non-stimulated strength and voluntary strength training. Therefore, I won’t be discussing electrical stimulation in any more detail.

**Principles of progressive resistance training**

There are many different ways to increase strength; one of the more commonly used ways is progressive resistance strength training. This involves contracting muscles against progressive levels of resistance. Typically, this is done using three sets of 10 contractions in one training session. The training is performed two-three times a week for at least 12 weeks (i.e., 90 maximal contractions per week) (73).

Most of what we know about the effectiveness of progressive resistance training in non-paralysed muscles comes from the vast amount of literature on progressive resistance strength
training in able-bodied individuals (73-79). These studies have examined many different training parameters and all indicate progressive adaptations in muscular strength and performance with training. However, there is some debate about some of the more subtle aspects of optimal training and very little is known about the responsiveness of partially paralysed muscles to any type of strength training. Therefore, even though the focus of my thesis is predominantly on partially paralysed muscles, a lot of this first chapter draws on what is known about strength training in non-paralysed muscles.

**Training variables in able-bodied individuals**

The evidence in able-bodied literature suggests that the amount of strength gains is dependent on the type of program used, in particular the training variables chosen. These training variables include the type of muscle action, intensity (amount of load), exercise selection, rest periods between sets, volume (sets and repetitions) and frequency (74). The next few paragraphs will provide a summary of some of the current literature on progressive resistance strength training principles in terms of these variables. It is from this literature that strength training programs have been formulated for people with SCI but it is not clear whether this is appropriate. It is also important to note that there is considerable debate around these training variables and the most effective training program to improve strength in the able-bodied population. For example the American College of Sports Medicine (ACSM) advocates moderate loading (60%-70% of 1 RM) and multiple sets to improve strength (80). However, this has been challenged by some (81-83) who believe that loads as low as 30% of maximum strength are equally effective at driving exercise-induced muscle changes. Regardless of the ongoing debate around some of the subtleties of resistance training programs, we do know that long-term progressive resistance training leads to an increase in muscle strength and hypertrophy (79, 84-88).
Muscle action

Training can include the use of eccentric, concentric and isometric muscle actions as well as bilateral and unilateral single and multiple joint exercises. There are some benefits to training a muscle eccentrically. These include greater force production per unit of muscle size than either concentric or isometric actions (89). Eccentric training can overload the muscle and therefore has the ability to enhance muscle mass, strength and power (90). Eccentric contractions can also generate high mechanical muscle tension at a low metabolic cost (91). They require less motor unit activation per specific load (89), however often result in more pronounced delayed onset muscle soreness (92) as compared with concentric actions. Most programs will include both concentric and eccentric actions in a given repetition. However, including additional isometric exercises may be beneficial (93).

Concentric and isometric contractions were used in both Project One and Two. This decision was not based on the able-bodied literature. Rather, it was based on a recent study conducted in patients following SCI by Jayarman (95), which used both types of contractions. Jayarman compared an isometric training program to a conventional progressive resistance-training program in people with incomplete SCI. The overall peak torque of the lower limbs for the isometric training group increased from 34 ± 15 to 54 ± 28 Nm compared with the conventional training group who did not change (32 ± 14 to 32 ± 13 Nm). However this was only a small pilot study hence these findings needed to be further explored.

Loading and repetitions

It is clear that manipulating the training load can stress the muscle in very different ways. It is thought that there is a direct relationship between the training load and the muscular adaptive response (96). Traditionally, it has been thought that a resistance-training program using low
repetition/high resistance favours improvements in strength/power and that training with high repetition/low resistance increases muscular endurance (97). Many studies have been conducted to test this hypothesis (74, 77). Anderson and Kearney tested this theory by investigating the effects of three different training programs on strength changes (98). Forty-five college-aged men were randomly allocated to 3 different types of strength training: high resistance/low repetitions, medium resistance/medium repetition and low resistance/high repetition. They performed the training for nine weeks, three days/week and it was found that the high resistance/low repetition group showed the greatest increases in maximal strength (20% increase compared to 8% and 4%, respectively) and the least improvement in endurance compared to the other two groups (24% increase compared to 39% and 41%, respectively). No measures of variability for the change data were provided. Stone and Coulter found comparable results in 45 college-aged women who were assigned to similar groups with the only difference being the low resistance/high repetition group performed only one set of 30-40 RM compared to one set of 100-150 RM (99). They also found that the high resistance/low repetition training resulted in greater strength increases than the medium resistance/medium repetition and low resistance/high repetition training (19% increase compared to 17% and 12%, respectively, p < .001) and that the low resistance/high repetition training produced greater muscle endurance gains in the lower body than the medium resistance/medium repetition and high resistance/low repetition training (137% increase compared to 80% and 84%, respectively, p < .001). Similarly, no measures of variability for the change data were provided.

Studies have also been conducted to understand the intramuscular adaptations in response to different training loads. A study using a similar design to the two previous studies with three different training groups; low, intermediate and high repetitions and a control group who did
no exercise used muscle biopsy to analyse fibre-type composition, CSA, myosin heavy chain (MHC) content and capillarization (100). They found that all three major fibre types (types I, IIA and IIB) hypertrophied in the low repetition and intermediate repetition groups, where as they found no significant increases in either the high repetition or control group.

A study by Munn et al examined the effect of the number of sets and contraction speed on strength (101). One hundred and fifteen healthy, untrained participants were randomised to either a control group or one of four training groups. The different training groups were; one set fast, three sets fast, one set slow and three sets slow. The training consisted of three sessions per week over six weeks. They found that three sets of training produced greater strength gains compared to a single set, with an average increase of strength of 48% (2.66 kg, 95% CI 1.40 to 3.94 kg). They also found that fast training resulted in an average of 11% (0.64 kg, 95% CI 0.01 to 1.27 kg) greater strength increase than slow training. Rhea et al found similar results with a 12-week training program comparing three sets to one set for bench press and leg press exercises (102). They found the one set group showed increases of 26% (SD 5) for leg press while the three set group increased by 56% (8), which was significantly different.

The ACSM (80) recommends loads corresponding to an 8- to 12-repetition maximum (RM) be lifted one to three sets, training two or three days each week to optimise muscular strength. An 8RM to 12RM load is the amount of weight a person can lift through full range of motion 8 to 12 times before they fatigue.

In both Project One and Two (94), the resistance was applied by the hands of the therapists. This was because it is very difficult to establish an 8 to 12 RM in a person who has profound
neurological weakness. Therapists ensured that the resistance applied exhausted participants by the end of each set of 10 contractions and hence mimicked a 10 RM. We chose four sets; two sets of isometric and two sets of concentric contractions in line with previous strength training studies in the SCI population (95, 103).

**Exercise selection**

Multiple modalities can also be used in order to target single or multiple joints, for example, free weights, machines, cords or body weight exercises. Multiple-joint exercises such as sit to stand or squats require complex neural responses (104). Single-joint exercises, such as extending or flexing the knee, can be used to target individual muscle groups. Another way to vary the level of muscle activation is to train bilaterally versus unilaterally. Unilateral training may lead to increases in bilateral strength and bilateral training may lead to increases in unilateral strength (74).

In both Project One and Two (94) we chose to train single joint muscles to make it easier to measure the changes in strength. This was the simplest way to train without using weight machines, pulleys or cords, as it is often difficult to ensure maximal resistance is applied throughout range in very weak muscles that are partially paralysed.

**Rest periods**

Another important factor that affects the muscles reaction to resistance exercise is the rest period between sets. Most clinical trials have shown larger strength gains with long versus short rest periods e.g. 2-5 minutes vs 30-40 seconds (105). It is thought that strength recovery may not be complete with a shorter rest period (106). One study showed minimal strength increases with a 40 second rest period (107). Participants were randomised into two groups; one had a long rest period (160 seconds) while the other group had a short rest period (40
seconds). They performed strength exercises for 4 weeks, three days/week. The short rest period group only showed strength gains of 0.7% (2.2, SEM) for the quadriceps muscle, whereas the long rest period group showed increases of 5.9% (2.5, SEM).

In both Project One and Two (94) we allowed a two-minute rest in between each set of 10 exercises to improve performance for subsequent sets.

**Frequency**

Optimal progressive resistance training frequency (the number of workouts per week) depends upon several factors such as the type of exercise performed, the individual's level of experience, the number of muscle groups trained, and intensity of the training. It is important that the rest period between sessions is long enough to allow muscles to recover and to avoid overtraining, however not too long to cause detraining (108). A 48-hour rest period is generally recommended, which allows for training three days/week (108-110). A meta-analysis of 140 studies was performed to determine the dose response for strength development (111). The data for frequency showed that strength gains were greatest with a frequency of 3 days per week in the untrained individuals (effect size (posttest mean-pretest mean/pretest SD), 1.9, SD 2.3). It is thought that one-two days/week is effective for maintaining strength in individuals who are already engaged in a strength-training program (112). Contrary to this, a paper by Taaffe et al also demonstrated that training once or twice per week can be just as effective as three times per week in improving strength in able bodied men and woman aged 65-79 years (113). This again highlights the conflicting evidence surrounding the most effective principles of progressive resistance strength training. In both Project One and Two, (94) participants trained three days/week.
Measuring strength

Measuring strength in the SCI population is used for monitoring recovery, loss of motor function and evaluating therapeutic interventions. There are several methods to measure strength some of which are quick and easy to administer, others, which are time consuming and require expensive equipment. This section of the thesis will outline the commonly used methods of measuring strength, including the advantages and limitations of each method.

One repetition maximum (1RM)

A 1RM is a measurement of the maximum load that can be lifted throughout range once only. A 1RM can be used for many different exercises such as chest press, lat pull-down and bicep curls depending on the muscles to be tested. This method can be difficult to measure because the weight must be increased until the person fails to complete a full contraction through full range. This is challenging, as it requires a trial and error approach. Consequently, patients need to attempt lifting many different weights until the true 1RM is reached. This process can often fatigue the patient and therefore reduce the likelihood of obtaining a true 1RM. The other limitation of this method is that it has been found to be susceptible to systematic bias meaning group means often increase in the second testing session. This “learning” effect can lead to increases in the group means as high as 5% (114). Familiarising individuals with the exercise technique has been trialed to minimise this systematic bias, however it often still remains (114). In an RCT, both groups are exposed to the “learning” effect thereby minimizing any systematic bias.

Dynamometry

There are two types of dynamometers; hand-held (a portable device) or large commercially available isokinetic dynamometers. Hand-held dynamometers are easy to use, portable, compact, less time-consuming and cheaper compared to isokinetic dynamometers (115-118).
Isometric strength is measured when the length of the muscle remains relatively static while force is produced. This type of test requires the participant to push or pull against a fixed interface, usually either a hand-held dynamometers or isokinetic dynamometer. A systematic review in 2014, included 54 studies investigating the intraexaminer reliability of hand-held dynamometry (119). Twenty-six studies demonstrated adequate reliability (ICC>0.90). However, only 7 of these studies were of high quality showing acceptable reliability for elbow flexion and extension. The most common methodological limitations were absence of blinding and lack of variance in testing order. The authors found that all other movements showed unacceptable reliability. The results of this systematic review are limited to the elbow joint in able-bodied participants. In one study, the able-bodied participants were very young children (age range, 28-50 months). In four of the other high quality studies the professions of the examiners were unknown. It is not possible to generalise these results to a neurological population with significant weakness. The authors stated that the sources of error could have been due to the length of time to produce a maximum contraction, the strength of the examiner to resist the participants’ muscle contractions, standardization of the position of the participant, the joint or examiner, proximal joint stabilization, placement of the dynamometer or failure to maintain a constant lever arm length. These sources of error may be even more pronounced in a person with neurological weakness.

Isokinetic dynamometers can also measure isokinetic strength. Isokinetic strength is measured when an individual actively shortens or lengthens a group of muscles while the limb is moved at a constant angular velocity. Isokinetic dynamometers can measure various muscle groups at different angular velocities. A systematic review and meta-analysis consisting of 8 articles investigated the reliability of muscle strength assessment in patients with chronic post-stroke...
hemiparesis using isokinetic dynamometry (120). The studies looked at a range of joints; knee, ankle, hip, shoulder and elbow. The knee joint was the most commonly tested with six of the eight articles studying strength measurements for both knee flexion and extension (121-126). The studies found high reliability, irrespective of the type of contraction, speed and whether it was the affected or non-affected side. The overall results of the review suggested that there was good to excellent reliability of measuring muscle strength in both the affected and non-affected side of the upper and lower limbs using isokinetic dynamometry with the lowest ICC being 0.69 (95% CI 0.59 to 0.79) for ankle plantar flexion and the highest ICC being 0.97 (95% CI 0.94 to 1.00) for knee extension. However, it is thought that isokinetic dynamometers may not be appropriate for testing the strength of very weak muscles where movement against resistance is not possible (127). Therefore, other measurement tools may be more appropriate such as MMT.

**Manual muscle testing (MMT)**

Manual muscle testing is another way to measure strength. Manual muscle testing is a method for assessing the strength of individual muscle groups based on the muscles ability to move in relation to gravity and manual resistance (22). Manual muscle testing has been considered a useful diagnostic and prognostic tool that can be used to examine the effectiveness of therapeutic interventions. Manual muscle testing has been around for a long time. It was first developed by Lovett and described by Wright in 1912 (128) and has since been revised and adapted resulting in several different variations (129-134). Each variation has a slightly different scale to represent each grading criteria, although all methods have similar criteria to define each grade. The grading criteria are based on factors such as gravity, the amount of range the limb can move through and the amount of force applied by the examiner. Commonly known methods have been described by Kendall and McCreary (135) and Daniels and
Worthingham (136)(Table 1). Kendall and McCreary use percentages to define their criteria whereas Daniels and Worthingham use words (Normal, Good, Fair, Poor, Trace, or Zero). The other most commonly used method is the Medical Research Council (MRC) scale (137) which uses numerical grades 0 to 5 (Table 1). The guidelines for the scale also state that plus and minus subdivisions can be used within the grade 4.

Table 1: Medical Research Council, Daniels and Worthingham and Kendall and McCreary scales

<table>
<thead>
<tr>
<th>Medical Research Council (137)</th>
<th>Daniels and Worthingham (136)</th>
<th>Kendall and McCreary (135)</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Normal (N)</td>
<td>100%</td>
<td>Holds test position against maximal resistance</td>
</tr>
<tr>
<td>4</td>
<td>Good (G)</td>
<td>80%</td>
<td>Holds test position against moderate resistance</td>
</tr>
<tr>
<td>3</td>
<td>Fair (F)</td>
<td>50%</td>
<td>Holds test position against gravity</td>
</tr>
<tr>
<td>2</td>
<td>Poor (P)</td>
<td>20%</td>
<td>Able to move through full ROM gravity eliminated</td>
</tr>
<tr>
<td>1</td>
<td>Trace (T)</td>
<td>5%</td>
<td>No visible movement; palpable or observable tendon prominence/flicker contraction</td>
</tr>
<tr>
<td>0</td>
<td>Zero (0)</td>
<td>0%</td>
<td>No palpable or observable muscle contraction</td>
</tr>
</tbody>
</table>

It was not until the poliomyelitis era when there were large numbers of patients with significant neurological weakness that the clinimetrics of MMT started to be examined. This was due to an increase in clinical drug trials where strength was a key outcome (138, 139). It was in 1954 when Lilienfeld and colleagues examined the inter-rater reliability of MMT grades in a gamma globulin clinical trial (140). Forty-five individuals with poliomyelitis were examined and a total of 65 muscles per patient were assessed. The examiners had different
educational backgrounds; 43 physical therapists, 23 physicians and 8 nurses. The average differences in muscle strength scores between the examiners ranged from 3% to 9.1%. The authors did not state how they calculated the percentage differences. It was concluded by the authors that MMT was a reproducible measurement tool, which could be used by examiners with differing educational backgrounds.

More recently the inter- and intra-rater reliability of MMT has been assessed in various patient populations (129-132, 141-143). One study assessed the inter-rater reliability of the 6-point MRC scale on both simulated and real patients recovering from critical illness across 26 muscle groups (141). The simulated participants mimicked a wide range of strength following training from a physiotherapist. The raters were 19 trained personnel with various professional backgrounds; five physicians, four nurses, two respiratory therapists, five physiotherapists, one pharmacist and two research assistants. They also used a sole reference rater who was an experienced physiotherapist with >30 years experience in using and teaching MMT. They found for all 26 muscles, the median (interquartile range) values for the percent agreement and ICC were 96% (91 to 98%) and 0.98 (0.95 to 1.00) demonstrating excellent reliability. It is important to acknowledge the limitations of this study; approximately half of the participants were able-bodied individuals who were mimicking patients. The authors did state they performed a subgroup analysis with the 9 real patients and found that the results for this subgroup were consistent with the results from the overall analysis, however the small sample size makes interpretation of the results difficult.

A systematic review by Dekkers et al in 2014 examined the clinimetric properties of tools for measuring upper limb muscle strength for children with cerebral palsy (CP) (144). They found one study investigating the inter-rater and test-retest reliability of MMT in the upper limb
muscles of children with CP (145). For test-retest reliability, ICC values ranged between 0.88 and 0.96 and for inter-rater reliability, ICC values ranged between 0.60 to 0.91. However, this study rated only “fair” on the COSMIN score; a checklist used to assess the methodological quality of the studies.

**Evidence about effectiveness of strength training in SCI**

Strength training comprises a large component of rehabilitation programs for people with SCI. Franz et al conducted a large observational multicentred trial in which data were collected about the type of therapies administered over a 3-year period (146). Physical and sports therapists across 6 SCI rehabilitation units recorded all administered physical and sport therapies. They found strength training was the most commonly used intervention contributing to 30% of all interventions. We know physiotherapists dedicate large amounts of time to strengthening muscles with the ultimate goal of improving function that is meaningful, however little is known about the most effective ways to strengthen partially paralysed muscles. In fact, very few randomised controlled trials have investigated the effectiveness of progressive resistance training in people with SCI, which is the most commonly used strength training paradigm. Since 2008 there has only been three clinical trials, which have compared progressive resistance to usual care (94, 103), progressive resistance training and electrical stimulation to usual care (147) and two different types of strength training programs (95) to increase strength in partially paralysed muscles.

Two of these trials looked at the effect of progressive resistance training on partially paralysed muscles alone in people with SCI. The first randomised controlled trial compared a progressive resistance exercise program to no training in 32 people with tetraplegia. The training consisted of 3 sessions a week for 8 weeks. Each session involved three sets of 10 repetitions of either
the wrist extensor or flexor muscles. The progressive resistance exercise program was performed with a device specifically designed for very weak muscles to allow participants to move through full range in an anti-gravity position. The authors did not find a clear therapeutic benefit in the wrist muscles of people with tetraplegia (mean (95% CI) between-group difference was 0.2Nm (-0.5 to 0.8)) (103). However, many participants in this trial had less than grade 3/5 strength. It was therefore hypothesised that progressive resistance training may not be effective in those with insufficient neural drive to stimulate the types of peripheral adaptations commonly associated with gains in strength in able-bodied people. It could also be possible that the training program was not long enough.

To explore this issue further a second clinical trial was conducted looking at the effectiveness of progressive resistance training in partially paralysed muscles of people with SCI but in muscles which were stronger and larger than those used in the first trial. Participants were randomised to receive either electrical stimulation muscle contractions in combination with progressive resistance training to their quadriceps muscle or no training (control). The training consisted of three sessions a week for 8 weeks. The primary outcome was voluntary quadriceps strength. The results indicated a small treatment effect, although the estimate of the effect was imprecise (mean (95% CI) between-group difference was 14Nm (1 to 27)) (148). A further complication to the interpretation of this trial was the addition of electrical stimulation (ES) to the progressive resistance training program. This made it impossible to determine whether the ES or progressive resistance training, or both, were the essential aspects of the training program.

A small cross-over trial of 5 participants has since compared two types of strength training in the lower limbs of people with incomplete SCI (95). It compared progressive resistance
training versus maximal isometric strength training. Interestingly, the authors failed to demonstrate any within-group changes in strength from progressive resistance training but impressive within-group changes in strength with maximal isometric strength training. The between-group differences were statistically significant although it was difficult to determine the size of the treatment effect. The statistically superior effects of maximal isometric strength training over traditional progressive resistance training is difficult to explain and may reflect bias or the idiosyncrasies of the testing protocol. Nonetheless this trial, especially in the light of the previous two trials, raises questions about the responsiveness of partially paralysed muscles to different forms of strength training.

More recently a systematic review was conducted which examined the effectiveness of all types of physiotherapy interventions for increasing voluntary muscle strength in people with SCI including all the studies mentioned above (149). It included randomised controlled trials of physiotherapy interventions for people with SCI. Two comparisons were chosen: physiotherapy interventions compared with sham or no intervention, and physiotherapy interventions compared to each other. The primary outcome was voluntary strength of muscles directly affected by SCI. Twenty-six trials were identified which met the inclusion criteria and provided usable data. They examined four comparisons, namely, resistance training versus no training; resistance training combined with electrical stimulation versus no training; a package of physiotherapy interventions including locomotor training versus no training; and robotic gait training versus overground gait training. A statistically significant between-group difference was found for all four comparisons. The authors concluded that a limited number of physiotherapy interventions increased voluntary strength in muscles directly affected by SCI. However, it was also noted that the results were not convincing due to the limited number of trials and imprecise estimates. The authors acknowledged that of the 26
trials, 12 rated high for risk of bias on three or more items of the Cochrane Risk of Bias Tool. Common sources of bias were failure to conceal allocation, blind participants and personnel, and blind assessors. It is important also to note that all studies included participants with varying degrees of neurological weakness making it impossible to ascertain how effective physiotherapy interventions are at increasing voluntary strength in very weak muscles (grade 3 and below on MMT) compared to stronger muscles (grade 3 and above on MMT). This systematic review challenges the long held belief that physiotherapy interventions are effective at increasing strength of muscles affected directly by SCI and that we should not assume that all “strengthening” interventions are effective.

A fourth trial compared progressive resistance training to no training (150), however the researchers trained partially paralysed and fully innervated muscles. The results showed that performing strength training twice a week for 9 months significantly increased upper body muscle strength. The largest between-group difference was in the left chest press (mean between-group difference was 10kg, 95% CI, 3 to 17). It is worth noting that these strength increases were gained with a training program of twice per week, which is less than the commonly used three per week in most published studies in this population.

Hicks’ study also had two methodological weaknesses, which could contribute to bias. The first being the lack of blinded assessors to group allocation and secondly being the large drop out rate of 32% at 9 months. There was also large variability in the way participants responded to the strength training as seen in the wide 95% confidence intervals about the estimate of the treatment effects.
Evidence about effectiveness of strength training in other neurological populations

With limited studies examining the effects of progressive resistance training following SCI, we need to look to studies investigating resistance training in other neurological conditions. Central nervous system disorders such stroke, cerebral palsy (CP) and multiple sclerosis (MS) all lead to significant weakness and thus strengthening interventions are also widely used.

A systematic review investigating the effects of progressive resistance training in people with multiple sclerosis found 16 studies which all reported an increase in muscle strength in the trained muscles (151) ranging from ~7% to 21% for knee extensor (152-156), knee flexor (152) and plantar flexor (157) muscles.

Four systematic reviews have all determined that progressive resistance training is effective in the stroke population (158-161). The most recent systematic review included 11 studies involving 314 participants. It included only randomised or quasi-randomised trials. The mean PEDro score was 6.3 (range 3 to 8). Points were lost for lack of concealed allocation with only 45% of studies reporting this and only 36% carrying out an intention-to-treat analysis. The results showed large effects of progressive resistance training on strength (standardised mean difference, 0.98 (95% CI, 0.67 to 1.29, I² = 0%)) compared with no intervention or placebo (160).

In contrast, two systematic reviews examining the effects of strength training in children and adolescents with cerebral palsy found limited evidence to support the efficacy of strength training for improving strength (162, 163). The most recent of these reviews reported strengthening interventions had only a very small effect on strength (standardised mean
difference, 0.20 (95% CI, -0.17 to 0.56)) and walking speed (mean difference, 0.02 m/s, (95% CI, -0.13 to 0.16)). It was concluded that strengthening interventions are neither effective nor worthwhile.

We can look to the evidence in other neurological populations to guide the way in which we train muscles in people following SCI, however it is important to note each disorder has a different underlying pathophysiology. This means muscles may respond differently. For example following a stroke the brain has the ability to change the properties of its neural circuits. This is known as brain plasticity and it has been shown that rehabilitation may modify and encourage the neuronal plasticity processes (165, 166). It is less clear how much neural plasticity occurs in the spinal cord. The underlying mechanisms for increasing strength in partially paralysed muscles in people following a SCI are not well understood. Therefore, to further understand the mechanisms that are potentially responsible for strength increases in partially paralysed muscles, we need to understand the physiology that limits force production in an intact nervous system.

**Possible mechanisms underlying strength gains**

The ability for an able-bodied person to voluntarily produce muscle force has been studied extensively. A key finding from these studies is that the production of muscle force may be limited by both central and peripheral mechanisms. That is, force production can be limited by the ability of the central nervous system to drive motorneurons (central limitation) or by the intrinsic force-generating capacity of the muscle itself (peripheral limitation) (167). Gandevia defined central mechanisms as those involving structures that act proximal to the neuromuscular junction and peripheral mechanisms as those involving the structures that act distal to the neuromuscular junction (167).
Central mechanisms can be quantified by measuring activation using twitch interpolation techniques. Twitch interpolation involves delivering an electrical stimulus to the motor nerve during a maximal voluntary contraction, producing a twitch-like increment in force (168). The amplitude of this “interpolated twitch” is then used to measure voluntary “activation” of muscles. This technique commonly shows that full activation of the muscle is not possible during a maximal effort: typically force increments of 2-5% of maximal force are observed immediately following stimulation.

There are many different peripheral factors that have been suggested to contribute to force production. Possible factors are hypertrophy, myofibrillar packing density, fibre type shifts or extracellular lateral force transmission. However, it is likely that physiological cross sectional area (PCSA) is the most important peripheral determinant of muscle force generating capacity (169). Physiological cross sectional area can be calculated by studying muscle architecture. The force of a contraction is a function of the number of cross-bridges formed between actin and myosin filaments (170). The more cross-bridges that are formed, the stronger the force contraction. Therefore, the force contraction is dependent on the number of actin and myosin filaments arranged in parallel. Filament spacing is approximately constant, so the PCSA provides a rough measure of the number of actin and myosin filaments arranged in parallel. The PCSA is the area of a slice that passes transversely through all of the fibres of a muscle so, on theoretical grounds, should be a strong predictor of muscle force (172, 173). This is why we chose to measure PCSA using magnetic resonance imaging (MRI) to see if we could detect a change in muscle architecture as a result of strength training.
Both central and peripheral factors limit force production in able-bodied individuals with an intact nervous system. This is evident from observations of centrally mediated neural drive obtained using twitch interpolation (174-177) and observations of peripheral changes obtained by measuring PCSA (178, 179). However, central and peripheral limitations to muscle force are less understood in a neurological population where there is disruption to the central pathways and atrophy.

Any increase in force due to strength training in able-bodied individuals can therefore be split into peripheral and central adaptations. As outlined above these can be measured in various ways. There continues to be disagreement around what stage these mechanisms precisely occur during a strength-training period and about how much we can attribute strength gains to each factor.

**Muscle architecture**

There are many different ways in which we can study peripheral adaptions to strength training. Some peripheral adaptations can be understood by studying muscle architecture. Skeletal muscles are composed of muscle fascicles, which are groups of several hundred muscle fibres. Muscle architecture refers to the size and arrangement of these fibres in a muscle relative to the axis of force generation, and is unique to each muscle. Muscle architecture is important as it is closely linked to the function of a muscle. There are different arrangements of these fibres depending on the muscle. Two common arrangements are fusiform and pennate. In fusiform muscles, the fascicles are parallel to the long axis of the muscle (for example, vastus intermedius). In pennate muscles, fascicles are at an angle to the axis of force generation of the whole muscle (for example, rectus femoris, vastus lateralis and vastus medialis). This arrangement allows more fibres to be packed within a given volume and
therefore allows higher force production than a fusiform arrangement of muscle fibres.

Studying architectural differences tells us about the force generating capacity of that muscle.

Muscle architecture changes with age (181, 182), training (183), injury (184) and disuse (185).

The typical muscle architectural measurements are fibre length, pennation angle and physiological CSA (PCSA). The fibre length is the distance between the insertions of the fascicles into the upper and deeper aponeuroses measured in millimeters. The pennation angle is the angle between a fascicle’s orientation and the tendon axis measured in degrees.

Physiological CSA is the sum of the CSAs of each fibre in the muscle. Physiological CSA is calculated by dividing the volume by the fibre length (186). Many people have previously studied CSA under MRI (33, 38, 187-190) to examine the effects of SCI or therapy interventions on muscle architecture. However, these studies measured anatomical CSA (ACSA) not PCSA. There is only a very weak relationship between PCSA and ACSA.

**Methods to measure muscle architecture**

**Ultrasonography**

Frequently, muscle architecture has been studied with ultrasound imaging. This technique is relatively inexpensive and non-invasive. However, there are many limitations to this method. Ultrasound imaging only produces a two-dimensional (2D) image (191, 192) and is susceptible to measurement error. Accurate measurements are subjective to the position of the probe, requiring the probe to be held perpendicular to the aponeuroses and aligned with the fascicles (191). Furthermore, the probe can compress the skin, which can change the underlying architecture of the muscle. The major concern is that there is no standardised method to determine the optimal probe orientation, so there is no accepted solution to minimise the
measurement error (194-196). Therefore, a more accurate and reliable method for measuring muscle architecture is needed.

**Magnetic Resonance Imaging (MRI)**

Magnetic resonance imaging is a non-invasive, three-dimensional (3D) imaging method. It does not expose participants to harmful radiation, instead the images are based on the presence and properties of water (or, more precisely, hydrogen protons). Magnetic resonance imaging uses external magnetic fields to create high-resolution images, which allows good contrast between soft tissues. These images are created from measurements of the radio-signals emitted when hydrogen protons change orientation. The signal intensity depends on the hydrogen concentration or proton density: the higher the proton density, the stronger the signal intensity.

Magnetic resonance imaging is able to distinguish between fat, connective tissue and muscle tissue making it a suitable measurement tool for determining the overall structure of skeletal muscle (197, 198). The advantages of MRI over ultrasound are that it can image both superficial and deep structures, and it has a 3D field of view that allows production of larger images. This is particularly important when imaging larger muscles such as the quadriceps muscles.

One limitation of MRI is its long acquisition time (198). This makes measuring muscle architecture during contraction or during movement difficult. Even when taking measurements under static, passive conditions, participants must remain still and relaxed throughout the scanning time. Another limitation to MRI is that it can’t measure individual fibres. Pennation angles and fascicle lengths cannot be measured directly from anatomical MRI.
scans. However, with the advancement of MRI techniques such a diffusion tensor imaging (DTI), it is now possible to measure muscle architecture indirectly (199).

**Diffusion Tensor Imaging (DTI)**

Diffusion tensor imaging (DTI) is an MRI technique, which allows the measurement of the amount and direction of diffusion of water molecules. Diffusion tensor imaging has traditionally been used to reconstruct the anatomy of the brain, which is helpful for diagnostic and treatment purposes in neurological conditions such as a stroke. More recently, DTI has been applied to study skeletal muscle physiology, anatomy and pathology. Diffusion tensor imaging has become increasingly popular as it can obtain diagnostically relevant imaging readouts of skeletal muscle structure that are difficult or impossible to obtain with other techniques (199).

The cylindrical shape of muscle fibres, means diffusion tends to occur more longitudinally down the fibre than across the fibre. Diffusion tensor imaging measures this anisotropic diffusion in hydrogen atoms, and then the primary direction of diffusion per pixel or voxel can be calculated. The primary direction of diffusion is thought to be aligned with the muscle fibres. Fibre tractography algorithms are then used to fit a curved line through the tracts and extend them to the aponeuroses in order to represent muscle fascicles (200). It is then possible to create a 3D muscle image and from this image muscle architecture measurements can be obtained.

In a clinical setting, DTI can be applied to study muscle damage caused by pathology at the fascicular level (199). Diffusion tensor imaging is sensitive to changes in tissue microstructure and concurrently allows for quantification and visualization of the macroscopic muscle architecture (201). There has been an increase in the number of studies utilising DTI to
measure architectural parameters (200, 202-207). However, DTI has not yet been used to measure muscle architecture of partially paralysed muscles in people with SCI following a strength-training program.

A limitation of DTI is its low signal to noise ratio. The tractography algorithms require a set of stopping criteria to determine the start and endpoints of fascicles (202). This criterion is somewhat arbitrary and can result in unrealistically long or short fibre tracts (208, 209). Diffusion tensor imaging scans are typically of lower resolution than anatomical scans. However, recently a method has been developed to overcome some of these limitations. High-resolution anatomical scans can be used to provide clear muscle boundaries allowing fascicle endpoints to be identified. Consequently, more accurate measurements of fascicle lengths and other muscle architectural parameters can be obtained (202).

**Effects of SCI and resistance training on intramuscular fat**

The composition of a muscle is an important determinant of a muscle’s functional capacity. One component of muscle is fat. Intramuscular fat (IMF) is typically defined as fatty infiltration of a muscle, which is storage of lipids in adipocytes underneath the deep fascia of muscle. Fatty infiltration can compromise the force-producing capacity of a muscle due its effects on the number of half-sarcomeres, an important determinant of force production (210).

Following a SCI, a person will accumulate large deposits of adipose tissue within and between the muscle groups of the lower extremities, this can be up to four times the amount compared to an able-bodied individual (33, 211, 212). Accumulation of IMF not only affects the muscle’s force-generating capacity, it also increases a person’s risk of multiple medical complications such as impaired glucose tolerance, metabolic disorders and diabetes (33, 213). With an
increased life expectancy following SCI and an increase in older adults sustaining a SCI, chronic disease is expected to become more prevalent in this patient population (214). Therefore, it is important to investigate the effects of interventions on reducing accumulation of IMF in order to maintain the force-generating capacity of the muscle and potentially reduce the risks of cardiovascular diseases.

Some evidence suggests that resistance training can reduce IMF. One study looked at the effects of resistance training on IMF in an elderly population (215). They trained 13 healthy men and women aged 65-83. Each participant had a computed tomography (CT) scan performed following 24 weeks training, 24 weeks detraining, and 12 weeks retraining. IMF was defined by measuring muscle density, often termed muscle attenuation. Skeletal muscle attenuation was measured in Hounsfield Units (HU), which was obtained for the quadriceps and hamstrings. Strength changes were accompanied by alterations in muscle density. Quadriceps HU decreased by 7.7±1.0% (SE) following detraining, suggesting an increase in the relative amount of IMF. In addition, quadriceps HU increased by 5.4±0.5% (SD) with retraining, suggesting a reduction in IMF. Jones and Rutherford reported similar results following 12 weeks of resistance training in young adults, with increases of 3.5%-5.9% (216).

The main limitation for both of these studies is that they quantified IMF with CT. These measurements of muscle density are typically taken from discrete sites throughout the muscle and not the whole muscle. This can be problematic, as it has been shown that IMF is not distributed evenly throughout muscles (217), and so may not accurately quantify whole muscle fat.
There are many other ways to measure the amount and distribution of fat. Dual-energy X-ray absorptiometry (DXA) measures total body fat but says little about fat distribution within muscles. Magnetic resonance imaging (MRI) techniques have also been used to quantify IMF (218-221). T1-weighted MRI images have been used in previous studies to calculate the cross sectional area of intramuscular fat (222). This process separates fat from contractile tissue based on presumed differences in image intensity of fat and contractile tissue. This can be problematic, as the measurements are based on an arbitrary threshold separating the tissue types. T1-weighted imaging cannot detect small concentrations of lipid within muscle (less than 3% volume fraction)(223). The accuracy of the fat images can also be influenced by magnetic field inhomogeneities of the scanner (224). Such limitations have led people to increasingly use mDixon protocols to quantify IMF (218, 225-227). mDixon techniques use the chemical shift difference between fat and water to reconstruct separate water and fat images. This provides an estimate of the amount of fat in a given voxel, as well as the anatomical distribution of IMF. Muscle biopsy can also be used to quantify lipid content within tissues. However, contamination of extracellular lipid or connective tissue in the sample may confound the measurement. A true reflection of intracellular concentration of lipid can be obtained using a histological approach. This approach quantifies skeletal muscle fibres (cells) with an oil red O staining method using human biopsy samples (228, 229).

**Summary and key research questions**

Neurological weakness following SCI is one of the main impairments affecting a person’s functional capacity. Many interventions are used to increase strength of partially paralysed muscles (103, 147, 230, 231), however the most commonly used is progressive resistance training. There have been no randomised trials to date, which have investigated the efficacy of progressive resistance training for increasing voluntary strength in partially paralysed
muscles. Furthermore, there have been no studies to date to investigate the mechanisms responsible for strength gains in partially paralysed muscles nor have there been studies investigating the effects of progressive resistance training on IMF in partially paralysed muscles.

Three of the studies in this thesis were designed to determine the efficacy of progressive resistance training in strengthening partially paralysed muscles of people with SCI, the mechanisms responsible for strength gains and the effects of training on IMF. The fourth study was designed to test the reliability of a commonly used strength assessment, the 13-point MMT. The key research questions investigated in this thesis are as follows:

Chapter 2:
• Does 12 weeks of strength training combined with usual care increase the strength of partially paralysed muscles of people with recent SCI more than usual care alone?
• Does strength training improve resistance to fatigue, change participants’ perceptions of strength and function and affect spasticity?

Chapter 3:
• Does muscle architecture change after short-term strength training in partially paralysed muscles of people with SCI?

Chapter 4
• Does 6 weeks of strength training reduce IMF in partially paralysed muscles of people with SCI or neurologically intact muscles of able-bodied individuals?
• Do people with SCI and partial paralysis have increased IMF compared to neurologically intact muscles of able-bodied individuals?

Chapter 5
• Is the 13-point MMT reliable?
Reference list

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Chapter 2 - Project One: strength training for partially paralysed muscles in people with recent spinal cord injury: a within-participant randomised controlled trial.

This study has been published. It is presented here in the Author Accepted Version format.


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Conference proceedings
This study has been presented at three conferences. It appears in the conference proceedings as:


Strength training for partially-paralysed muscles in people with recent spinal cord injury: a within-participant randomised controlled trial.

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Abstract

Study design: Within-participant randomised controlled trial.

Objectives: To determine whether strength training combined with usual care increases strength in partially-paralysed muscles of people with recent spinal cord injury (SCI) more than usual care alone.

Settings: SCI units in Australia and India.

Methods: Thirty people with recent SCI undergoing inpatient rehabilitation participated in this 12-week trial. One of the following muscle groups was selected as the target muscle group for each participant: the elbow flexors, elbow extensors, knee flexors or knee extensors. The target muscle on one side of the body was randomly allocated to the experimental group and the same muscle on the other side of the body was allocated to the control group. Strength training was administered to the experimental muscle but not the control muscle. Participants were assessed at baseline and 12 weeks later. The primary outcome was maximal isometric muscle strength, and the secondary outcomes were spasticity, fatigue and participants’ perception of function and strength.

Results: There were no dropouts and participants received 98% of the training sessions. The mean (95% CI) between-group difference for isometric strength was 4.3 Nm (1.9 to 6.8) with a clinically meaningful treatment effect of 2.7 Nm. The mean (95% CI) between-group difference for spasticity was 0.03/5 points (-0.25 to 0.32).

Conclusion: Strength training increases strength in partially-paralysed muscles of people with recent SCI although it is not clear whether the size of the treatment effect is clinically meaningful.

Sponsorship: Prince of Wales Hospital Foundation and National Health and Medical Research Council of Australia.
Keywords: strength, spinal cord injury, rehabilitation, physiotherapy
Introduction

Weakness secondary to partial paralysis is one of the most common impairments after spinal cord injury (SCI). Partial paralysis is caused by disruption to some but not all motor pathways. This type of weakness in the upper limbs can profoundly reduce hand function (1). Similarly, partial paralysis of the lower limb muscles prevents people from walking (2). The ability to walk and use the hands are both high priorities for people with SCI and important determinants of quality of life (3).

Many different interventions are used and advocated to increase strength (4). However, the most common type of strength training is progressive resistance training. This involves maximally contracting muscles against high levels of resistance. Typically, this is done in sets of 10 contractions. The sets are repeated three times in one training session, and training is performed three times a week for at least 12 weeks (i.e. 90 maximal contractions per week) (5). The basis for the belief that progressive resistance training is effective comes largely from trials involving people without paralysis (6, 7). However, it cannot be assumed that what is effective for muscles of able-bodied individuals is also effective for the partially-paralysed muscles of a person with SCI.

There are currently only three clinical trials that have examined the effectiveness of any type of strength training in the partially-paralysed muscles of people with SCI (8-10). The first randomised controlled trial involving the wrist muscles of people with SCI failed to find a clear therapeutic effect of progressive resistance training. However, many participants had strength of less than grade 3/5. It was hypothesised that progressive resistance training may not be effective in these very weak participants due to insufficient neural drive to stimulate muscle fibre hypertrophy (9). In those very weak people, repetitive practice with low
resistance may be more important because increases in strength may be largely secondary to neural adaptations (11). A second clinical trial examined the effectiveness of progressive resistance training and electrical stimulation (ES) in muscles which were stronger and larger than those examined in the first trial (8). The results indicated a treatment effect, although the 95% CI associated with the mean between-group difference was wide and failed to rule in or out the possibility of either a very small or very large treatment effect. In addition, the use of ES made it difficult to determine whether the ES, the progressive resistance training, or both, were the important aspects of the training program. More recently a small cross-over trial of 5 participants compared isometric strength training with concentric strength training in the lower limbs of people with incomplete SCI (10). Interestingly, the between-group difference indicates that isometric strength training is superior to concentric strength training. These results need to be replicated in a larger trial but nonetheless suggest that the type of muscle contraction used in strength training may be important.

While there are three trials examining the effectiveness of strength training, there is still considerable uncertainty about the responsiveness of partially-paralysed muscles to any type of strength training program. The aim therefore of this trial was to determine the effects of a 12-week strength training program on maximal voluntary isometric muscle strength. The secondary aims were to determine the effects of the training on spasticity, muscle fatigue and participants’ perceptions of strength and function. We restricted our study to muscles with grade 3/5 or 4/5 strength and included both isometric and concentric strength training because the tentative evidence to date supports the combination of this type of training in stronger muscles (10).
Method

An assessor blinded randomised within-participant controlled trial was conducted in five SCI units: four SCI units in Australia and one SCI unit in India. The first and last participants were randomised in September 2014 and November 2015 respectively. The start of recruitment at the five SCI units was staggered with the last SCI unit commencing recruitment in August 2015. One target muscle group was selected for each participant from the following groups of muscles: elbow flexors, elbow extensors, knee flexors or knee extensors but only if the corresponding contralateral muscle group had similar strength. If more than one muscle group was suitable for inclusion then the stronger muscle was chosen although the clinicians had some freedom to select a muscle based on their clinical judgment and the practicalities of implementing the trial protocol. Participants received a strength program for the target muscle group on one side of the body only (experimental side). The side receiving strength training was determined by random allocation.

The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12614000914662). All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed and the study was approved by the appropriate ethics committees.

Participants: Thirty in-patients with recent SCI were recruited (see Table 1 for the inclusion and exclusion criteria). A computer-generated blocked random allocation schedule was compiled prior to commencement by a person not involved in the recruitment of participants. Each participant was randomly allocated to train the target muscle in their left or right limb. Participants’ allocations were placed in opaque, sequentially numbered and sealed envelopes, which were held off site by an independent person. Once a participant passed the screening
process and completed the initial assessments, an envelope was opened and allocation revealed. The participant was considered to have entered the trial at this point.

**Intervention:** The target muscle group in the experimental limb was trained three times a week for 12 weeks following the key principles of progressive resistance training (12). Participants performed 40 maximal contractions in four sets of 10. The first two sets of 10 maximal contractions were isometric contractions and the second two sets of 10 were concentric contractions with a 2-minute rest after each set of 10 contractions. Each contraction was approximately 4 seconds in duration. Resistance was applied through the hands of the therapists to ensure the muscle contractions required maximal effort from the participants. Therapists tried to ensure that the resistance they applied exhausted participants by the end of each set of 10 contractions (13). If participants’ strength increased and the therapists were unable to provide sufficient resistance then weights were applied to the participants’ limb in addition to the resistance applied through the therapists’ hands. Therapists encouraged patients to maximally contract their target muscle throughout each training session.

All participants continued to receive usual care which involved comprehensive rehabilitation. This involved gait and functional training for activities of daily living as considered necessary by their treating therapists (e.g. training to transfer, walk, roll and push a manual wheelchair). Participants received other forms of therapy deemed appropriate for managing fitness, respiratory compromise, contractures, spasticity or pain. In addition, participants were able to receive any type of strength training program deemed appropriate by their treating therapists to other muscles groups on both sides of the body with the exception of the target
muscle group. The treating therapist was blinded to whether the left or right side of the target muscle group was receiving the strength training intervention.

**Assessment:** Participants were measured by a blinded assessor once prior to randomisation and once 12 weeks after randomisation (with a 1-week window). The success of binding was recorded. The primary outcome was maximal voluntary isometric strength. The secondary outcomes were spasticity, muscle fatigue and participants’ perceptions of strength and function.

The details of the outcome measures are as follows:

**Maximal voluntary isometric strength.** A dynamometer (Lafayette Instrument Company, Lafayette, Indiana) was used to measure peak isometric muscle strength with the knee or elbow stabilised in 90° flexion (14). The dynamometer was cradled in a custom-made rigid jig which allowed the participant to push or pull against a fixed interface. There were two jigs specifically designed for this study: one for the upper limb and one for the lower limb (see Figure 1). Strength was recorded in pounds and converted into Nm (using the perpendicular distance from the joint axis to the centre of the force transducer). Participants were required to perform six maximal isometric muscle contractions and were provided with verbal encouragement throughout. There was a 60-second rest between each trial. The left limb was always measured before the right limb. A between-group difference equivalent to 15% of mean initial strength was set as clinically meaningful prior to the commencement of the study.

**Spasticity.** Spasticity was included as a secondary outcome measure because some argue that strength training has deleterious effects on spasticity (15). The quality score of the Ashworth
Scale was used to measure spasticity in the participants’ target muscle group. Specifically, the quality of resistance felt when the limb was moved was recorded on a 5-point scale where 0 reflected “no increase in tone” and 4 reflected “limb rigid in flexion or extension”. It was decided prior to the commencement of the study that a between-group difference of 1 point would be considered indicative of a detrimental effect of strength training on spasticity.

**Muscle fatigue.** Muscle fatigue was measured using the dynamometer and jig as outlined above, however participants were required to perform repeated maximal isometric contractions of 4 seconds duration over 3 minutes with a 4-second rest between each contraction. The mean torque generated over the last three contractions was divided by the mean torque generated over the first three contractions to calculate the fatigue index (16). A between-group difference equivalent to 15% of the mean initial fatigue index was considered clinically meaningful.

**Participants’ perceptions of strength.** At the completion of the trial participants were asked to rate separately their impressions of change in strength in their right and left target muscle group on a 15-point scale where -7 indicated “a very great deal worse”, 0 indicated “no change” and +7 indicated “a very great deal better” (17). A between-group difference of 1 point was considered clinically meaningful.

**Participants’ perceptions of function.** At the completion of the trial participants were asked to rate separately their impressions of change in their ability to use their right and left target limb for functional activities on a 15-point scale where -7 indicated “a very great deal worse”, 0 indicated “no change” and +7 indicated “a very great deal better” (17). A between-group difference of 1 point was considered clinically meaningful.
In addition, participants were asked to rate the inconvenience of the training program. They rated the inconvenience on a 10-point scale, where 1 indicated the training was “extremely inconvenient” and 10 indicated that the training was “not at all inconvenient”.

**Statistical Analysis:**

STATA v13 was used for all analyses using intention-to-treat. The t-distribution was used to estimate mean between-group differences and associated 95% CI from the change data (i.e., post-intervention minus pre-intervention) or post-intervention data for outcomes without a baseline measure. To test the robustness of the assumptions about the normality of the distribution of the data, all analyses were repeated using the STATA “cendif” routine and bootstrapping techniques. The “cendif” routine is based on the generalized Hodges-Lehmann median differences function and makes no assumptions about the normality of distributions (18). The results from the additional analyses were almost identical and are not reported here.

**Results**

The flow of participants through the trial is shown in Figure 2. No participants withdrew from the study. The median (interquartile range, IQR) age and time since injury were 46 years (25 to 65) and 2 months (1.4 to 3.1), respectively. Participants had American Spinal Injury Association Impairment Scale (AIS) A (n= 8), AIS B (n= 1), AIS C (n= 11) or AIS D (n= 10) lesions with neurological levels ranging from C1 to L3 and motor levels ranging from C1 to L3 as defined by the AIS (see Table 2). The groups were similar at baseline for most key prognostic factors.
The protocol dictated that participants perform the progressive resistance strength training three times a week for 12 weeks with a total of 36 training sessions. This was largely achieved with a median (IQR) total number of 36 (35 to 36) training sessions provided over 12 weeks (equivalent to 98%). Training sessions were missed on public holidays or if participants were unwell. As far as possible, additional sessions were provided to make up for missed sessions. All assessors remained blinded for the 12-week outcome measure.

The mean (95% CI) between-group difference for maximal voluntary isometric strength was 4.3 Nm (95% CI, 1.9 to 6.8) but the 95% CI spanned the clinically meaningful treatment effect of 2.7 Nm, indicating that while strength training increased strength there is uncertainty about whether the size of the treatment effect is clinically meaningful. The mean (95% CI) between-group differences for perceived change in strength and function were 2.2 points (1.3 to 3.0) and 2.1 points (1.2 to 3.0) respectively, both indicating that participants not only perceived increases in strength and function but that these perceptions were also clinically meaningful. The mean (95% CI) between-group difference for spasticity was 0.03 points (-0.25 to 0.32), with the upper end of the 95% CI less than 1 point. This indicates that the strength training did not have deleterious effects on spasticity. The effects of strength training on fatigue were unclear with the 95% CI associated with the mean between-group difference spanning the clinically meaningful treatment effect (see Table 3).

The median (IQR) perception of inconvenience of the strength training was 9/10 (9 to 10), where a score of 10 indicates “not at all inconvenient”. There were no serious adverse events although one participant experienced quadriceps tightening and discomfort throughout his last week of training with the concentric contractions. This was resolved with applying less resistance and dissipated once the exercises were ceased.
Discussion

This study indicates that strength training increases strength in the partially-paralysed muscles of people with SCI. These results are important because weakness is a major problem for people with SCI and very little research attention has been directed at determining the effectiveness of different strength training paradigms. However it is not clear from our results whether the increases in strength are clinically meaningful because the 95% CI associated with the mean between-group difference spans our pre-determined clinically meaningful treatment effect. We set the clinically meaningful treatment effect at 15% of mean initial values. This was somewhat arbitrary but even if we had set it to a lower value, the interpretation of our results remains the same unless people consider a treatment effect as low as 1.9 Nm as potentially worthwhile. Interestingly, participants perceived that the intervention improved strength and function with the lower ends of the 95% CIs associated with the mean between-group differences above our pre-defined clinically meaningful treatment effects of 1 point. However, participants were not blinded so their perceptions may in part reflect preconceived ideas about the benefits of progressive resistance training.

The results of this study align with a similar study we conducted in people with grade 3/5 or 4/5 strength of the quadriceps muscles although in our earlier study we added ES to our strength training program (8). The main difference in results between the two studies is the precision of the treatment effect (reflected by the width of the 95% confidence interval associated with the mean between-group difference). The 95% confidence interval in this study (95% CI, 1.9 to 6.8 Nm) indicates more precision than in our earlier study (95% CI, 1 to 27 Nm). The tighter precision may reflect the larger sample size, the weaker participants or the within-group study design. While a within-group study design generally increases the precision of treatment estimates, it can also decrease treatment effects if training one limb has
a carryover effect onto the untrained limb (19). A larger trial using a between-group design would offer the best solution to both issues.

We included a measure of fatigue because we were interested in determining whether strength training reduces fatigue. However, our results were inconclusive failing to rule in or out a treatment effect on this outcome. A larger sample is required to provide a clear answer to this question. These results align with the results of our previous studies, which have all failed to demonstrate a clear treatment effect of any type of strength training on fatigue (8, 9). These results may reflect a problem with the way we measure fatigue. For example, fatigue may be better measured with repeated contractions over more than 3 minutes. Or perhaps we needed to keep participants naïve to the test to ensure that they did not deliberately pace themselves for the 3-minute test. Alternatively, our results may indicate that our strength training programs do not reduce fatigue. We know from able-bodied literature that the optimal training program for reducing fatigue involves more emphasis on repeated contractions and less emphasis on resistance (20). We may therefore need to incorporate these training principles to reduce fatigue. However, we need to be open to the possibility that partially-paralysed muscles do not respond in the same way to training as the non-paralysed muscles of able-bodied people and that it may be very difficult to reduce fatigue with any type of training.

The results of this study suggest no deleterious effects of strength training on spasticity. The 95% CI associated with the mean between-group difference indicates that these results cannot be dismissed on the basis of the sample size. However, these results need to be interpreted with caution because the target muscle of some participants may have been flaccid. This may in part explain the initial low levels of spasticity with mean Ashworth
values less than 1/5 points. In addition, we did not measure the spasticity of other muscles below the level of the lesion. So while there is mounting evidence both from our own previous trials (8, 9) and from trials in people with other types of neurological conditions (21, 22) to indicate that any remaining concerns that strength training increases spasticity are not justified, the results of this study probably can not be used to support this argument.

In our study, the therapists used their hands to provide the resistance. The training was provided in this way to ensure the muscle contractions required maximal effort from the participants. The participants were strongly encouraged to maximally contract their muscles throughout each training session particularly during the last few contractions of each set of ten. The downside of this method of strength training is that it is difficult to quantify the resistance provided by therapists. However, our results indicate that despite this disadvantage, participants got stronger. Perhaps if the training was provided in other ways or with commercially-available gym equipment then the treatment effects may have been even more convincing. The use of equipment decreases reliance on therapists and therefore is less costly. However, in our experience it is difficult to get the fine graduation in resistance required to ensure patients with neurologically induced weakness are maximally contracting throughout the 10 contractions. Future studies could further explore this issue.

One limitation of our study is that we only measured isometric strength even though our training involved isometric and concentric contractions. It would have been interesting to also measure strength during concentric contractions. We explored ways of doing this but it was not easy in the clinical setting, and it may not be necessary to measure both types of strength because they are strongly correlated (23, 24). It is somewhat surprising that a recent study indicated that strength training using isometric contractions was superior to strength training
using concentric contractions, and indicated no within-group changes in strength of those who only performed concentric contractions (10). The study was only small and needs verifying in a larger trial but nonetheless highlight how little is known about optimal strength training paradigms.

In conclusion, physiotherapists have administered strength training to non-paralysed muscles for a long time and have assumed that this intervention is equally applicable to partially-paralysed muscles but these assumptions have not been adequately tested. The results of this study provide some of the first evidence to indicate that partially-paralysed muscles are responsive to strength training. The results are not generalisable to grade 1 or grade 2 muscles and still indicate some uncertainty about whether the size of the treatment effect is clinically meaningful.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.
References

Table 1: Inclusion and exclusion criteria

**Inclusion:** Participants were included if they:

- Had a recent complete or incomplete SCI (as defined by the International Standards for Neurological classification of SCI) that was sustained less than one year prior
- Had bilateral partial paralysis in one of the target muscle groups (i.e. elbow flexors, elbow extensors, knee flexors or knee extensor muscles)
- Had a grade 3 or 4 strength in the target muscle group on both sides of the body
- Had neurological stability in the strength of the target muscle groups (i.e. not more than a 2/5 point change in MMT over the preceding 3 weeks according to medical records).
- Were an inpatient and were likely to remain in hospital for the duration of their involvement in the trial (i.e. approximately 13 weeks) or if discharged early could reasonably be seen as an outpatient.
- Were aged 16 years or over at the time of consent, willing to participate in the trial and free of any other type of neurological lesion.

**Exclusion:** Participants were excluded from the trial if they:

- Had any condition preventing testing or training of the target muscle group
- Were unable to co-operate (e.g. serious medical condition, cognitive impairment, drug dependency, psychiatric illness, or behavioural problems)
- Had insufficient English to provide informed consent.
Table 2: Characteristics of participants (n=30), including age, gender, time since injury, motor level on experimental side and control side, motor score, neurological level, AIS classification, muscle grade of target muscle group and muscle type (median and interquartile range, IQR) (MMT= manual muscle test)

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<tr>
<td>C5-8</td>
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<tr>
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<td>Knee flexors</td>
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<tr>
<td>Knee extensors</td>
<td>10</td>
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<tr>
<td>Time since injury (months), median (IQR)</td>
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<td>AIS classification, n</td>
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<td>C</td>
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<tr>
<td>Motor level, n</td>
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Typical setup

**Figure 1:** The upper (a) and lower limb (b) jig used to cradle the dynamometer.
**Figure 2:** Flow of participants through trial

- **Screened for inclusion (n=241 participants)**
  - Excluded (n = 211 participants)
    - Miscellaneous (n = 5)
    - Length of stay < 12 weeks (n = 30)
    - Not bilateral grade 3/5 or 4/5 strength (n = 129)
    - Medical or psychological disorder (n = 31)
    - Declined to be participate (n = 13)
    - < 18 years of age (n = 3)
- **Baseline Assessment (n=30 participants/60 limbs)**
- **Random allocation (n=30 participants/60 limbs)**
  - **Experimental limb: Strength training (n=30 limbs)**
  - **Control limb: No strength training (n=30 limbs)**
  - **Follow-up assessments (n=30 participants/60 limbs)**
  - **Dropouts (n=0)**
  - **Dropouts (n=0)**
Table 3: The intention-to-treat analysis. Mean (SD) pre- and post training for the experimental and control limbs with the mean (95% CI) between-group differences. The pre-defined clinically meaningful treatment effects are also indicated.

<table>
<thead>
<tr>
<th></th>
<th>Experimental limb</th>
<th>Control limb</th>
<th>Between-group differences</th>
<th>Clinically meaningful treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre training</td>
<td>Post training</td>
<td>Pre training</td>
<td>Post training</td>
</tr>
<tr>
<td>Maximal isometric strength, Nm</td>
<td>18.3 (10.7)</td>
<td>29.4 (15.4)</td>
<td>18.1 (11.4)</td>
<td>24.8 (15.6)</td>
</tr>
<tr>
<td>Spasticity, 0 to 5 points</td>
<td>0.57 (0.97)</td>
<td>0.76 (0.94)</td>
<td>0.63 (0.85)</td>
<td>0.8 (0.1)</td>
</tr>
<tr>
<td>Fatigue, ratio</td>
<td>0.94 (0.32)</td>
<td>0.92 (0.23)</td>
<td>1.0 (0.61)</td>
<td>0.9 (0.19)</td>
</tr>
<tr>
<td>Participants’ perception of function, -7 to +7 points</td>
<td>--</td>
<td>4.5 (1.7)</td>
<td>-</td>
<td>2.4 (2.4)</td>
</tr>
<tr>
<td>Participants’ perception of strength, -7 to +7 points</td>
<td>--</td>
<td>4.7 (1.01)</td>
<td>-</td>
<td>2.6 (1.9)</td>
</tr>
</tbody>
</table>
Chapter 3 - Project Two: a preliminary investigation of mechanisms by which short-term resistance training increases strength of partially paralysed muscles in people with spinal cord injury.

This study has been published. It is presented here in the Author Accepted Version format.


Conference proceedings
This study has been presented at two conferences. It appears in the conference proceedings as:


A preliminary investigation of mechanisms by which short-term resistance training increases strength of partially paralysed muscles in people with spinal cord injury

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Abstract

Study Design: Pretest-posttest design.

Objectives: To investigate mechanisms by which short-term resistance training (six weeks) increases strength of partially paralysed muscles in people with spinal cord injury (SCI).

Setting: Community-based setting, Sydney, Australia.

Participants: Ten community-dwelling people with partial paralysis of elbow flexor, elbow extensor, knee flexor or knee extensor muscles following SCI (range 5 months to 14 years since injury).

Methods: Muscle architecture and strength were assessed before and after participants underwent a six week strength-training program targeting one partially paralysed muscle group. The outcome of primary interest was physiological cross sectional area (PCSA) of the trained muscle group measured using magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI). Other outcomes were changes in mean muscle fascicle length, muscle volume, pennation angle, isometric strength and muscle strength graded on a 13-point scale.

Results: The mean increase in maximal isometric muscle strength was 14% (95% CI, -3% to 30%) and 1.5 points (95% CI, 0.5 to 2.5) on the 13-point manual muscle test. There was no evidence of a change in muscle architecture.

Conclusion: This study is the first to examine the mechanisms by which voluntary strength training increases strength of partially paralysed muscles in people with SCI. The data suggest that strength gains produced by six weeks of strength training are not caused by changes in muscle architecture. This suggests short-term strength gains are due to increased neural drive or an increase in specific muscle tension.
INTRODUCTION

Partial paralysis is one of the most common impairments experienced after spinal cord injury (SCI). Partial paralysis of a specific muscle is caused by disruption to some but not all the motor pathways to that muscle (1). The paralysis can occur at or below the level of injury. Partial paralysis manifests as weakness (a reduction in the ability to generate muscle force voluntarily), which can severely impair motor function (2).

Previous studies have demonstrated the effectiveness of strength training for improving voluntary strength in the partially paralysed muscles of people with SCI (3-5). For example, we conducted a randomized controlled trial in which participants underwent strength training for 12 weeks (3). Training increased strength by a mean of 4.3 Nm (95% CI; 1.9 to 6.8) or 24% of initial strength.

In able-bodied individuals (i.e., people without paralysis) the mechanisms that contribute to strength gains are quite well understood. Both central and peripheral factors induce gains in strength (6-8). It is thought that neural adaptations (central factors) occur soon after strength training is initiated. Substantial peripheral adaptations (such as muscle hypertrophy) are typically not observed until after six or eight weeks of strength training (9-13). However, we hypothesised that, in people who have partial paralysis and are very weak, hypertrophy might occur earlier than six weeks (14).

The mechanisms by which training increases strength in partially paralysed muscles following SCI are not known. However one small randomised trial (N = 9) used MRI to measure muscle anatomical cross-sectional area (ACSA) of completely paralysed quadriceps muscles before and after 12 weeks of training with neuromuscular electrical stimulation.
against resistance (15). Training increased the ACSA of the knee extensor muscles by 35% and increased the ACSA of the knee flexors by 16%. As this study used electrically stimulated contractions to increase the strength of completely paralysed muscles it is not possible to draw conclusions from this study about the response of partially paralysed muscles to voluntary resistance training.

A key issue in quantifying peripheral responses to training is the measurement of muscle cross-sectional area. The physiological cross-sectional area (PCSA) of a muscle is the area of a hypothetical slice that passes transversely through all of the fibers of the muscle (16, 17). It is the main peripheral determinant of the intrinsic force generating capacity of a muscle (16). The best way to calculate PCSA is to divide muscle volume by mean fascicle length. Usually muscle volume is measured with MRI, CT scans, or ultrasound imaging (18-20), and fascicle length is measured with ultrasound imaging (21). A limitation of ultrasound measurements of fascicle length is that they are obtained from planar (two-dimensional) images, usually at just one site in the muscle (22-24).

New methods, based on MRI and DTI, can be used to measure muscle fascicle length of whole muscles in three dimensions (25, 26). These methods potentially provide more accurate measures of PCSA than methods that use ultrasound measurements of muscle volume and muscle fascicle length. DTI has not been used yet to measure training-induced changes in muscle architecture in people with SCI.

We conducted a preliminary investigation of the mechanisms by which short-term voluntary strength training increases voluntary muscle strength in partially paralysed muscles following
SCI. A novel feature of this study is the use of MRI and DTI to measure changes in muscle architecture, such as changes in PCSA that may contribute to changes in strength.

METHODS

A single-group pretest-posttest study was conducted on community-dwelling people with chronic SCI. Participants trained a partially paralysed muscle group for six weeks. Muscle architecture was measured before and after training using MRI and DTI. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618001606279). All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed. The study was approved by the relevant ethics committees. Participants gave written informed consent.

Participants

Ten people with SCI were recruited from the community in Sydney, Australia. People were eligible to participate if they had any type of SCI (i.e., complete or incomplete as defined by the International Standards for Neurological classification of SCI (ISNCSCI), had partial paralysis (grade 1 to 4 strength on a 6-point manual muscle test (27)) in one of the target muscle groups (elbow flexor, elbow extensor, knee flexor or knee extensor muscles), were aged 18 years or over at the time of consent, were willing to participate in the trial, and did not have any neurological condition other than the spinal cord lesion. People were excluded if they had any condition preventing testing or training of the target muscle group (for example unstable fractures in the target limb or uncontrolled spasticity), had completed more than three consecutive weeks in the last 3 months of progressive resistance training for the target muscle group, were unable to co-operate, had insufficient
English to provide informed consent, or were expected to be unable to remain still in the MRI scanner for the duration of the scan.

**Intervention**

One target muscle group was selected for each participant from the following muscle groups: elbow flexors, elbow extensors, knee flexors or knee extensors. The selected muscle group was partially paralysed. If more than one muscle group was suitable for inclusion, we chose the muscle group expected to benefit most from strength training or the muscle group the participant most wanted to train. Participants trained the target muscle group on one side of the body, three times a week for six weeks. The training program adhered to the principles of progressive resistance training. Training consisted of forty maximal contractions in four sets of ten, with two minutes rest between sets. The first two sets of ten repetitions were isometric contractions and the second two sets of ten repetitions were concentric contractions. We chose to train participants using concentric and isometric contractions because the findings of a small crossover trial, one of the few trials of strength training in individuals with SCI, suggested isometric training produced larger increases in strength than concentric strength training (5). Resistance was applied manually by a therapist because, with very weak muscles, it is difficult or impossible to provide the target resistance using free weights or isokinetic dynamometry. The therapist ensured that the resistance was sufficient to exhaust the participant by the end of the set, so that the participant was unable to perform another intense contraction after the tenth. If, over the course of the training program, a participant’s strength increased to the extent that the therapist was no longer able to provide sufficient resistance, weights were applied to the participant’s limb to provide additional resistance. When training sessions were missed, additional sessions were provided to make up missed sessions.
Assessment

Participants had an MRI scan and underwent a strength assessment prior to commencing the strength-training program and 48-72 hours after the last training session. The outcome of primary interest was the PCSA of the trained muscle group. Other outcomes were mean fascicle length, muscle volume, mean pennation angle, isometric strength and muscle strength graded on a 13-point scale.

Muscle architecture (PCSA, mean fascicle length, muscle volume and pennation angle).

Participants were positioned supine on the MRI scanner bed. If scanning the hamstrings, a wedge was placed under the knee so that the thigh was suspended to avoid compression of the muscle from the weight of the leg. Scans were obtained at a single joint angle. The participant was asked to remain relaxed and still during the scan.

A 3 Tesla MRI scanner (Achieva TX; Philips Medical Systems, Best, The Netherlands) with a 32-channel cardiac coil was used to obtain mDixon, T1-weighted (Figure 1) and DTI images of the thigh from the proximal end of the femur to the top of the knee joint or for the upper arm from the proximal end of the humerus to the elbow joint. The following imaging parameters were used. mDixon: 2-point 3D multi-echo mDixon fast field echo (FFE) sequence, TR/TE1/TE2 = 5.9/3.5/4.6 ms, field of view (FOV) = 180×180 mm, acquisition matrix = 180×180 (reconstructed to 192×192), slice = 1 mm, number of slices = 320 and scan time of 334 seconds. T1-weighted: TSE sequence, TR/TE = 700/12 ms, FOV = 180×180 mm, acquisition matrix = 256×188 (reconstructed to 864×864), slice = 4 mm, number of slices = 80 and scan time of 250 seconds. DTI: EPI sequence, TR/TE = 9050/60 ms, diffusion gradient time Δ/δ = 29.6/8.2 ms, FOV = 180×180 mm, acquisition matrix = 80×78 (reconstructed to 112×112), slice = 5 mm, number of slices = 50, number of signal averages
= 4, b-value = 500 s/mm² (b0 with b = 0 s/mm²), number of gradient directions = 16 on a hemisphere, fat suppression: spectral attenuated inversion recovery (SPAIR) and scan time of 606 seconds. To correct for local inhomogeneities in the magnetic field, the DTI scan was preceded by a B0-calibration using the following settings: 3D FFE, FOV = 180×180 mm (reconstructed to 112×112), slice = 5 mm, number of slices = 50, TR/TE/ΔTE = 30/4.6/2.3 msec, NSA = 2. Total scan time was approximately 23 minutes per session.

Muscle segmentation. The quadriceps, hamstrings, biceps or triceps muscles were manually outlined (segmented) using imaging processing software (ITK-SNAP, www.itksnap.org). We manually segmented one of the (pre-or post-training) images for each participant and then used registration algorithms (Elastix) (28, 29) to segment the second image based on the first. Segmentation was carried out by a researcher who did not know whether the scan was obtained before or after training.

Muscle architecture measurements were extracted from the anatomical MRI scans and DTI data using methods described in more detail elsewhere (26). Briefly, three-dimensional muscle surface models were created from the muscle segmentations. Muscle volumes were defined as the volumes of the surface models. Deterministic DTI tractography algorithms were used to generate a large number of fibre tracts within a muscle. The fibre tracts were extended so that they terminated on the muscle surface or on intramuscular tendons, like real muscle fascicles (26). Fascicle reconstructions were only included if the angle between the slopes at either endpoint of a fascicle was between 135 and 180° (so that fascicles could not curve back in on themselves), and fascicles were longer than 20 mm and shorter than 200 mm, were extrapolated to the aponeuroses by less than 40% of their total length, and had curvatures less than 30/m. Reconstructions of all muscles were visually inspected by a team
of researchers who were blinded to whether the reconstruction was obtained before or after training. Reconstructions that showed unrealistic alignment of muscle fascicles or had a sparse distribution of fascicles were excluded from further analysis. The fascicle length and pennation angle of a muscle were calculated as the median fascicle length and pennation angle of all fascicles reconstructed in that muscle. To determine the effect of training, the mean measurement of muscle fascicle length or pennation of all muscles of all participants before training was compared to the mean value after training. Muscle volume was calculated by summing ACSAs. PCSA was calculated by dividing muscle volume by median fascicle length.

Muscle strength. Isometric strength of the target muscle was tested using a dynamometer (Cybex Norm with Humac, CSMi, Stoughton, MA, USA). Participants were positioned in the testing chair with the target limb firmly strapped to the dynamometer arm. They were asked to perform four maximal contractions, lasting about three to five seconds each, while being provided visual feedback of the torque they produced and verbal encouragement to push as hard as they could. A one-minute rest was given between contractions. The largest force measured during the four contractions was taken to be the participant’s isometric strength.

Muscle strength was also measured using a 13-point manual muscle test scale (see Table 2). This scale was adapted from the traditional 0 to 5 point manual muscle test by adding scale increments. The 13-point manual muscle test is better able to detect changes in strength of participants with very weak muscles than with dynamometry (27).
**Statistical Analysis**

*Effects of training.* The mean effects of short-term training on PCSA, mean fascicle length, volume and pennation angle were estimated from the mean changes over the training period. Confidence intervals were obtained using the t-distribution.

*Sample size.* Sample size calculations were based on the changes in ACSA with 12 weeks of training reported by Gregory et al (30). They reported mean (SD) changes in the ACSA of the ankle plantarflexor and knee extensor muscles of 14% (SD 4) and 8% (SD 2), respectively. If we conservatively assume the larger SD (4%), a sample size of 10 participants would provide a better than 90% power to detect an increase in cross-sectional area of 5% with a two-tailed paired-samples test and a rejection probability under the null hypothesis of 5%.

**RESULTS**

The demographic characteristics of the 10 participants are presented in Table 1. Most participants had chronic injuries, and all had incomplete injuries with neurological levels ranging from C3 to L1 and motor levels ranging from C3 to L3 as defined by the ISNCSCI.

The protocol dictated that participants train three times a week for six weeks (total 18 training sessions). This was largely achieved: a median of 18 training sessions (IQR 17 to 18) was provided over the six weeks. No participant withdrew from the study.

On average, muscle volume increased by 1% (95% CI, -5% to 6%), PCSA decreased by 5% (95% CI, -16% to 6%), mean fascicle length increased by 8% (95% CI, -7% to 24%) and mean pennation did not change (mean 0%; 95% CI, -12 to 13) in the trained muscle. None of these effects were statistically significant (p > 0.05; Figure 2 and supplementary data).
The mean increase in maximal isometric muscle strength measured using the isokinetic dynamometer was 14% (95% CI, -3% to 30%). The mean change in strength measured on the 13-point manual muscle test scale was 1.5 points (95% CI, 0.5 to 2.5).

DISCUSSION

This exploratory study constitutes a first step towards understanding the mechanisms by which short-term voluntary strength training increases the strength of partially paralysed muscles in people with spinal cord injury. To our knowledge, no previous studies have examined the effects of voluntary strength training on muscle architecture following SCI. We found that six weeks of strength training increased the isometric strength of partially paralysed muscles by on average, 14% and by 1.5 points on the 13-point manual muscle test scale. We did not set a minimally worthwhile treatment effect prior to the commencement of the study because the study was primarily designed to explain the possible mechanisms underlying strength changes. Nonetheless, most would consider an increase of 14% (as measured with dynamometry) and 11% (as measured with the 13-point manual muscle test) as probably meaningful for most patients. Interestingly, despite the increase in strength we found no evidence of a systematic change in muscle architecture. The observation that strength increased but muscle architecture did not suggests that the increases in strength were mediated by mechanisms other than by changing muscle architecture (e.g., muscle hypertrophy). One such mechanism could be an increase in muscle specific tension (i.e., an increase in the maximal force produced per unit of cross-sectional area.). The second possible mechanism could be by enhancement of the excitation provided by the nervous system to the muscle (neural drive). We cannot be sure how much each of these mechanisms contributed to the gains in strength as we did not measure specific tension or muscle activation.
The study had several limitations. We did not endeavor to conduct a parallel randomised controlled trial because that would have required a much larger number of scans and the cost of conducting and analyzing scans is high. We considered conducting a randomised crossover design but an analysis suggested the potential bias associated with any achievable washout period would probably be greater than the bias inherent in a (single-group) pretest-posttest design. Therefore, we used a pretest-posttest design. The lack of randomisation means that we cannot completely rule out the possibility that the findings were biased by changes in muscle architecture that would have occurred over time without training, or which were an artifact of repeated measurement. However majority of participants had chronic injuries, so it is unlikely that muscle architecture would have changed over a six week period. A larger randomised study with a control group would provide a more rigorous test of our findings.

Another limitation to the study, which may explain the lack of change in muscle architecture, is the short training period (six weeks). In able-bodied individuals, changes in muscle architecture are typically observed only after six or eight weeks of strength training. We thought that because these participants were initially weak, architectural changes may have occurred more quickly (14), but this does not seem to be the case. If we had trained our participants for longer periods, we may have observed muscle architectural changes. That does not negate the novelty of the study: no previous studies have examined the mechanisms by which voluntary strength training increases strength of partially paralysed muscles, so this finding – that strength increases produced in partially paralysed muscles by six weeks of training are not mediated by hypertrophy – is new.
We chose to train the participants using concentric and isometric contractions because the findings of a small cross over trial, one of the few trials of strength training in individuals with SCI, suggested isometric training produced larger increases in strength than concentric strength training (5). However, studies of able-bodied individuals suggest that eccentric contractions lead to larger hypertrophic responses than isometric and concentric exercise (31). Future studies could investigate whether concentric, isometric or eccentric exercise induces the most hypertrophy in people with SCI.

To our knowledge, this is the first study to use DTI to measure muscle architecture in people with SCI. It is more difficult to segment MR images of skeletal muscles from people with SCI than from able-bodied individuals, perhaps because the muscles of people with SCI may be severely atrophied and appear to contain more fat. To reduce the errors that would otherwise result from comparing pre- and post-training images, we manually segmented one of the (pre-or post-training) images for each participant and then used automated algorithms to segment the second image based on the first, which meant that muscle borders were segmented consistently, if not accurately.

We used DTI to measure muscle architecture because DTI allows for non-invasive study of muscle fibre architecture and is not associated with radiation risks. Unlike ultrasound imaging, DTI is able to generate measurements in three dimensions from the whole muscle (24). However, DTI suffers from a low signal-to-noise ratio. Noise in the computed tensor fields can lead to poorly reconstructed muscle fiber fields and may cause error in measurements of muscle architecture. Our PCSA measurements are also potentially problematic as we measured PCSA by dividing volume by fascicle length at a particular joint angle rather than at optimal fascicle length. Measuring optimal fascicle length would have
been ideal, but currently it is not possible to measure fascicle lengths at optimal fascicle length in human muscles in vivo. Nonetheless, the MRI images allowed us to obtain good measurements of muscle volume and anatomical cross-sectional, and these measurements were not changed by six weeks of training. This increases our confidence in the conclusion that short-term training did not appreciably change muscle architecture.

In conclusion, we did not find any evidence that six weeks of strength training changed the architecture of partially paralysed muscles of people with SCI. Given the limitations of our measurements it is not possible to definitively conclude that short-term training did not increase PCSA. However, the fact that muscle volumes, which can be measured accurately from MRI, did not change strengthens the conclusion that peripheral adaptations made little or no contribution to increases in strength. Strength gains produced by six weeks of strength training of partially paralysed muscles of people with SCI are likely the result of improved neural drive to muscles or increases in specific muscle tension rather than changes in muscle architecture.
DATA ARCHIVING
Data set available in supplementary material.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ACKNOWLEDGEMENTS
We thank all our participants who gave up their time to contribute to the study. We would also like to thank Fernanda Di Natal for her assistance with the study.

FUNDING
The National Health and Medical Research Council and icare.

AUTHORS CONTRIBUTIONS
EAB and RDH came up with the study concept. All authors developed the study design and protocol. EAB collected the study data. All authors, were involved in the analysis and interpretation of data. EAB prepared the first draft of the manuscript. All co-authors provided input and critical review of the manuscript leading to the final version. All authors read and approved the final manuscript.
REFERENCES


Table 1: Characteristics of participants (n=10).

<table>
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<th>Characteristic</th>
<th>Value</th>
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<tr>
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</tr>
<tr>
<td>Sex (F:M)</td>
<td>3:7</td>
</tr>
<tr>
<td>Neurological level</td>
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</tr>
<tr>
<td>C1-4</td>
<td>3</td>
</tr>
<tr>
<td>C5-8</td>
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</tr>
<tr>
<td>T1-S5</td>
<td>6</td>
</tr>
<tr>
<td>Trained muscle</td>
<td></td>
</tr>
<tr>
<td>Elbow flexors</td>
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</tr>
<tr>
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<td>Knee flexors</td>
<td>6</td>
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<td>Knee extensors</td>
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<tr>
<td>Time since injury (years), median (IQR)</td>
<td>1.9 (1.1 to 3.9)</td>
</tr>
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<td>AIS classification</td>
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<td>B</td>
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<td>C</td>
<td>4</td>
</tr>
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<td>D</td>
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<td>Motor level</td>
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<td>2</td>
</tr>
<tr>
<td>C5-8</td>
<td>2</td>
</tr>
<tr>
<td>T1-S5</td>
<td>6</td>
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Table 2: 13-point manual muscle test

<table>
<thead>
<tr>
<th>Grade</th>
<th>Function of Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0 No palpable contraction</td>
</tr>
<tr>
<td>1</td>
<td>1 Visible or palpable contraction but unable to move</td>
</tr>
<tr>
<td>1+</td>
<td>2 Able to move through a <strong>small</strong> range (&lt;50%) with gravity eliminated</td>
</tr>
<tr>
<td>2−</td>
<td>3 Able to move through a <strong>large</strong> range (= or &gt;50%) with gravity eliminated</td>
</tr>
<tr>
<td>2</td>
<td>4 Able to move through <strong>full range</strong> of (=100%) with gravity eliminated</td>
</tr>
<tr>
<td>2+</td>
<td>5 Able to move through a <strong>small</strong> range (&lt;50%) against gravity</td>
</tr>
<tr>
<td>3−</td>
<td>6 Able to move through a <strong>large</strong> range (= or &gt;50%) against gravity</td>
</tr>
<tr>
<td>3</td>
<td>7 Able to move through <strong>full range</strong> (=100%) against gravity</td>
</tr>
<tr>
<td>3+</td>
<td>8 Able to move through full range (=100%) against gravity with <strong>small</strong> resistance through <strong>small</strong> range (&lt;50%)</td>
</tr>
<tr>
<td>4−</td>
<td>9 Able to move through full range (=100%) against gravity with <strong>small</strong> resistance through <strong>large</strong> range (= or &gt;50%) OR against gravity with moderate resistance through <strong>small</strong> range (&lt;50%)</td>
</tr>
<tr>
<td>4</td>
<td>10 Able to move through full range (=100%) against gravity with <strong>moderate</strong> resistance through <strong>full</strong> range (=100%)</td>
</tr>
<tr>
<td>4+</td>
<td>11 Able to move through full range (=100%) against gravity with <strong>maximal</strong> resistance through range (&lt;100%)</td>
</tr>
<tr>
<td>5</td>
<td>12 Normal strength</td>
</tr>
</tbody>
</table>
Figure 1: Example of transverse slices from the (A) T1-weighted scan and (B) mDixon scan (water image) obtained approximately mid-thigh in one participant. (C) Example of a three-dimensional reconstruction of the surface and fascicles of the biceps femoris longhead. The T1-weighted image is shown as well.
Figure 2: Pre- and post-training measurements of muscle volume, PCSA, median fascicle length, median pennation angle and strength in all 10 participants. Bars and error bars are means and SDs. Data from individual participants are shown with participant-specific symbols. Abbreviations: KE, knee extensors, KF, knee flexors, EF, elbow flexors
Chapter 4 - Project Three: intramuscular fat in people with spinal cord injury and able-bodied individuals before and after strength training.

Draft manuscript

Bye EA, Eguchi J, Bolsterlee B, Thom JM, Herbert RD Intramuscular fat in people with spinal cord injury and able-bodied individuals before and after strength training.
Intramuscular fat in people with spinal cord injury and able-bodied individuals before and after strength training

Running title: Intramuscular fat after strength training

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e-mail: r.herbert@neura.edu.au
Abstract

Study Design: Secondary analysis of data from two pretest-posttest studies.

Objectives: To compare the amount of intramuscular fat in neurologically intact muscles of able-bodied individuals and partially paralysed muscles of people with spinal cord injury (SCI), and to determine the effects of a strength-training program on intramuscular fat in the two groups.

Setting: Research institute, Australia.

Participants: Ten individuals with complete or incomplete SCI and eleven able-bodied individuals.

Methods: Participants with SCI underwent 6 weeks of supervised strength training for one partially paralysed muscle group. Able-bodied individuals underwent 8 weeks of supervised strength training for the knee extensor muscles. Intramuscular fat was assessed at baseline and after training using MRI (mDixon scans).

Results: Participants with SCI had a median of 14% (IQR 12 to 22%) intramuscular fat. Able-bodied individuals had a median of 8% (IQR 6 to 10%) intramuscular fat. The median difference in intramuscular fat (6%, 95% CI 3 to 15%) was significant (p = 0.002) and did not appear to be confounded by age or gender. Training did not produce a discernable change in intramuscular fat in the able-bodied individuals (mean 0.4%; 95% CI, -1.6% to 0.8%) or in the individuals with SCI (mean 0.1%; 95% CI, -1.2% to 1.0%).

Conclusion: Partially paralysed muscles of people with SCI have more intramuscular fat than neurologically intact muscles. A 6 to 8 week strength-training program does not produce discernable changes in intramuscular fat in either the partially paralysed muscles of individuals with SCI or the neurologically intact muscles of able-bodied individuals.
INTRODUCTION

The functional capacity of skeletal muscle is dependent on a number of factors including its composition. One of the constituents of muscle is fat. Intramuscular fat (IMF) is found both in (intracellular) and around (extracellular) muscle fibres (1). It has been shown, using needle biopsies, that on average 1.7% of the cross-sectional area of muscle fibres in lean adults and 3.2% of the cross-sectional area of muscle fibres in obese adults is occupied by lipid aggregates (2). Magnetic resonance spectroscopy studies have shown that the extracellular space has similar concentrations of fat to the intracellular space, and that high levels of total body fat and central adiposity are associated with high concentrations of intracellular and extracellular lipid in muscle (3).

The ability of a muscle to produce force is dependent on the number of half-sarcomeres arranged in parallel. Muscles with large physiological cross-sectional areas (PCSAs) tend to have many half-sarcomeres arranged in parallel and thus tend to have a high intrinsic force-generating capacity (4). Fat infiltration reduces the number of half-sarcomeres in parallel per unit PCSA, compromising the intrinsic force-producing capacity of the muscle (1).

It is challenging to study the effects of fat distribution on muscle force generating capacity because it is impossible to independently manipulate the amount and distribution of fat in a muscle. Consequently Rahemi and colleagues used continuum muscle models to simulate the effects of the amount and distribution of intramuscular fat on muscle force generating capacity (1). They found that fatty muscles produced less force per unit of fibre cross-sectional area than lean muscles (1). This was thought to be because fat increases passive muscle stiffness. They also found that the distribution of fat influenced the muscle’s capacity to generate force. The reduction of force was more pronounced when the fat was dispersed throughout the muscle than when the fat was localised at one site.
Following SCI, skeletal muscles atrophy (5, 6) and body composition changes (7), presumably in response to immobilization or disuse (8-10). Castro and colleagues showed that the average cross-sectional area (CSA) of atrophied skeletal muscle in people with SCI was 45-80% of that in age- and weight- matched controls 24 weeks after injury (9). Others have shown that atrophied skeletal muscles of people with complete SCI contain accumulations of IMF (11, 12). Gorgey et al studied people with incomplete SCI and found that, 6 weeks after injury, the cross-sectional area of IMF in thigh muscles was 126% larger than in able-bodied controls (5.2 ± 1.3 versus 2.3 ± 0.6 cm², mean ± SE) (13). They also found that relative IMF (i.e., IMF CSA/muscle CSA × 100%) was three-fold higher in the people with SCI than their able-bodied counterparts (5.8 ± 1.4% versus 2.0 ± 0.6%). The relative IMF continued to increase over a 3-month period in the individuals with SCI (to 8.6 ± 2.5%). In addition to the reduction in force-generating capacity of muscles, increased proportions of IMF after SCI likely contribute to secondary complications such as reduced insulin sensitivity (11, 12), impaired glucose tolerance, metabolic disorders and diabetes (12-15).

Some evidence suggests that resistance training can reduce IMF. A study of 32 older able-bodied individuals (>55 years old) found that 12 weeks of resistance training produced a significant decrease in the cross-sectional area of fat in the thigh (11%) and an increase in thigh lean tissue (7%) as measured with MRI, no measures of variability were reported (16). Another study, which examined the effects of a period of resistance training followed by a period of detraining and then a period of retraining found that quadriceps density decreased by 7.7 ± 1.0% (mean ± SE) following detraining and increased by 5.4 ± 0.5% with retraining (17). This was measured using computer-tomography, where an increase in muscle density suggests a reduction in the relative amount of IMF. To our knowledge, the effects of strength training on IMF have not been studied in people with SCI.
The aims of this study were to compare IMF in neurologically intact muscles of able-bodied individuals and partially paralysed muscles of individuals with SCI, and to determine the effects of strength training on IMF in both able-bodied individuals and people with partially paralysed muscles after SCI.

METHODS
We conducted secondary analyses on MRI data obtained from two training studies (18). The first study involved training partially paralysed muscles of the upper and lower limbs of 10 people with SCI. One partially paralysed muscle group (either elbow flexors, elbow extensors, knee flexors or knee extensors) was trained for a period of six weeks using progressive resistance training (details below). The second study involved neurologically intact muscles of eleven able-bodied individuals who completed eight weeks of progressive resistance training of the quadriceps muscles of both legs (only left leg was assessed). Both studies used a pretest-posttest design and were conducted on community-dwelling individuals in NSW, Australia. IMF was measured before and after training using mDixon MRI. To test the reliability of the mDixon scans we repeated four of the pre scans for four of the able-bodied individuals. All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed. The studies were approved by the relevant ethics committees. Participants gave written informed consent.

Participants

Study one: Participants were recruited by health professionals in the community or in outpatient clinics. People were eligible for inclusion in the study if they had any type of SCI (i.e., complete or incomplete as defined by the International Standards for Neurological classification of SCI), had a partially paralysed muscle (Grade 1 to 4 on manual muscle testing), were aged 18 years or over at the time of consent, were willing to participate in the trial and were free of any other type of
neurological lesion other than SCI. They were excluded if they had any condition preventing testing or training of the muscle group, for example unstable fractures in the target limb or uncontrolled spasticity.

**Study two:** Participants were staff and students from Neuroscience Research Australia and University of New South Wales who were aged 18 years or over at the time of consent, were healthy and willing to participate in the trial. They were excluded if they had conducted strength training in the last 12 months, were taking medication/supplementation that could influence muscle mass; were pregnant; had any chronic diseases or had MRI-incompatible implants (e.g. pacemaker, any implants containing ferromagnetic material).

**Intervention**

**Study one:** The muscle group was trained three times a week for six weeks. Training consisted of forty maximal contractions in four sets of ten. The first two sets of ten exercises involved isometric contractions and the second two sets of ten exercises involved concentric contractions. Resistance was applied through the hands of a therapist.

**Study two:** The quadriceps muscle group was trained three times a week for eight weeks. Training consisted of forty contractions in four sets of 8 to 12 repetitions to failure of bilateral leg press and leg extension using MAXIM Platinum Leg Extension/Curl and MAXIM Platinum Leg Press/Squat machines (Maxim Strength Fitness Equipment, South Australia, Australia).

**MRI data acquisition**

Participants underwent an MRI scan prior to commencing their strength training programs and 48-72 hours after the last training session. Participants were positioned supine on the MRI scanner bed. If the hamstrings were scanned, a wedge was placed under the knee joint so that the hamstrings were
not deformed by compression from the weight of the leg. For all other muscle groups, participants were positioned supine. Scans were obtained at a single joint angle under passive conditions. The participants were asked to remain relaxed and still during the scan.

A 3-Tesla MRI scanner (Achieva TX; Philips Medical Systems, Best, The Netherlands) with a 32-channel cardiac coil was used to obtain a 3D multi-echo 2-point mDixon Fast Field Echo (FFE) scan. 300 transverse anatomical images were obtained covering the entire cross-section of the thigh or upper arm. The settings of the mDixon scan were: FFE sequence, FOV = 180 × 180 mm², acquisition matrix = 180 × 180 (reconstructed to 192 × 192), TR/TE1/TE2 = 6.2/3.5/4.6 msec, voxel size = 0.94 × 0.94 × 1 mm³, number of slices = 320 and scan time of 355 seconds.

**Muscle segmentation**

The muscles in the trained muscle group were manually outlined (segmented) on all of the slices of the anatomical scans that the muscle was visible on using image processing software ITK-SNAP (www.itksnap.org). Manual segmentation was performed on the images from one scan chosen at random (either before or after training) for each participant. The images from the second scan were segmented using non-rigid registration algorithms (Elastix v4.7) (19, 20) which automatically mapped the boundaries of the muscles from the first scan to the boundaries of those muscles on the second scan. All segmentations were visually inspected and, when necessary, manually corrected. The researcher who performed the manual segmentation was blind to whether the scan was obtained before or after training.

**Quantification of fat**

The mDixon scans provided fat and water images, from which the fat fraction was calculated for each voxel by dividing the signal intensity from the fat image by the sum of the signal intensity of
the water and fat image (21). The average fat fraction of the trained muscle pre and post training was calculated as the average fat fraction of all voxels in the muscle, excluding voxels which included the boundary of the muscle. Pre training scans were repeated the day after the first scan to assess reliability in four of the neurologically intact participants.

**Muscle strength**

Maximal isometric muscle torque output was measured in the trained limb using a dynamometer (Cybex Norm with Humac, CSMi, Stoughton, MA, USA). Each participant was seated on the chair of the dynamometer. The seat position and length of the dynamometer arm was adjusted to match the participant’s body size. The positioning was recorded and reproduced for the post training assessment. Participants were instructed to push against the testing device “as hard as possible” for five seconds, while receiving visual feedback of the torque and verbal encouragement from the experimenter. After one familiarisation trial, three maximal contractions were recorded with one minute break between contractions for study one, and two minutes break for study two. The highest recorded peak torque of the three contractions was used as the isometric strength of the participant.

In study one, muscle strength was also measured using a 13-point manual muscle test (22). The 13-point scale is an expanded version of the traditional 6-point Medical Research Council scale and is better able to detect changes in strength in participants with very weak muscles (23).

**Statistical Analysis**

The mean effects of training on the proportion of IMF and strength were estimated from the mean changes in the trained muscles over the training period. Confidence intervals were obtained using the t-distribution. We also performed a post-hoc regression analysis of the pre training fat level on age in
the participants with SCI (see Discussion). Data are expressed as means ± standard deviation and confidence intervals unless stated.

RESULTS

A total of 22 participants were recruited for the two studies. Twelve were able-bodied individuals, one of whom withdrew due to an injury unrelated to the study. Ten were participants with SCI all of whom completed the study. Characteristics of the 21 participants who completed the training are shown in Tables 1 and 2.

The participants in study one participated in a median (IQR) of 18 training sessions (17 to 18) in six weeks (the target for study one was 18 sessions in six weeks). All of the participants in study two completed 24 training sessions in eight weeks.

In study one, the mean increase in maximal isometric muscle strength was 14% (95%, CI -3 to 30%) measured using an isokinetic dynamometer and 1.5 points (95% CI 0.5 to 2.5) measured on the 13-point manual muscle test scale. In study two, the mean increase in maximal isometric muscle strength was 12% (95% CI 4% to 20%).

Prior to training the participants with SCI had a median of 14% (IQR 12 to 22%) IMF and the able-bodied individuals had a median of 8% (IQR 6 to 10%) IMF (Figure 2). Data from SCI participants were highly skewed. Some participants with SCI had very high levels of IMF (Figure 2). The median difference in IMF (6%, 95% CI 3 to 15%) was significant (p = 0.002).
The proportion of IMF did not change with training in the people with SCI (0.1%, 95% CI, -1.2% to 1.0%; Figure 1) or in the able-bodied individuals (0.4%, 95% CI, -1.6% to 0.8%; Figure 1) (p > 0.05).

For the four participants we repeated their pre training scan, the average absolute difference in IMF between the first and second scans was 0.3% ± 0.3%.

DISCUSSION

The first finding of this study is that people with SCI had more IMF in their partially paralysed muscles than in the muscles of able-bodied individuals 14% (IQR 12 to 22%) compared to 8% (IQR 6 to 10%). We considered the possibility that this effect could be confounded by age, as the people with SCI were on average 22 years older (Figure 2) and previous studies have shown increases in the proportion of IMF with age (24-28). However, a post-hoc regression of the pre training IMF on age in the participants with SCI estimated that the effect of age on IMF was just 0.2% per year and this effect was not statistically significant. It should also be noted that the able-bodied individuals had a greater proportion of females than the participants with SCI (9/11 able-bodied females, 3/10 females with SCI). One MRI study found that males had significantly more IMF in the calf muscles than females (9.7% in males, 3.9% in females 29). However, in another post-hoc analysis, we found no evidence of a confounding effect of gender: a linear model with robust standard errors that included terms for both group and gender found non-significant effects of gender and significant effects of group. This was true even if the analysis was conducted on log IMF.

Our second finding was that a 6-8 week strength-training program did not change IMF in partially paralysed and neurologically intact muscles. This contrasts with the findings of other researchers. Marcus et al (30) trained 32 older adults (mean age 69 years) for 12 weeks and found a significant
11% (p<0.05) decrease in the cross-sectional area of intramuscular fat in thigh muscles. They may have seen a decrease in fat, when we did not, because they used a longer training period (12 weeks vs. 6 and 8 weeks in the present studies). Also, they used T1-weighted MRI images while we used mDixon images. Rather than quantifying the proportion of fat in muscles, they calculated the cross sectional area of intramuscular fat by separating fat from contractile tissue based on presumed differences in image intensity of fat and contractile tissue. This could be problematic, as the measurements will depend on the threshold separating the tissue types. Another limitation to T1-weighted imaging is that small concentrations of lipid within muscles (less than 3% volume fraction) cannot be detected (31). T1-weighted imaging is also subject to magnetic field inhomogeneities of the scanner, which may influence the accuracy of the fat measurements (32).

Another reason we may not have seen a decrease in IMF in the people with SCI is because they were too weak to elicit any changes due to limited neural drive. A combination of strength training and electrical stimulation may have a greater effect on IMF. However, the neurologically intact muscles did not change either suggesting even with a fully innervated muscle it is very difficult to reduce IMF.

Others have defined IMF by measuring the density of muscle, often termed muscle attenuation (33-35). Skeletal muscle attenuation has been measured using computed tomography (CT). Jones and Rutherford reported an increase in muscle density of 3.6%-5.9% following 12 weeks of resistance training in young adults (34), suggesting a reduction in the relative amount of IMF. Similarly, Sipila and Suominen found an increase in muscle density of 11.2% (35) after 18 weeks of strength and endurance training in elderly women.
Quantifying IMF with CT also has its limitations. Like T1-weighted MRI imaging, the measurements depend on the intensity threshold. Estimates of muscle density are typically measured from discrete sites throughout the muscle and not the whole muscle. Hasson et al (36) showed that IMF is not distributed uniformly throughout muscles, and so accurate quantification of fat ideally involves sampling the whole muscle.

Increasingly, mDixon protocols have been used to quantify IMF (37-40). MDixon techniques have been shown to be valid (41-43), repeatable (44), and reproducible (37). We repeated the pre-training scans of four able-bodied individuals and found an average absolute difference in estimates of IMF of 0.3%, demonstrating good reliability.

In conclusion, the partially paralysed muscles of people with SCI contain more IMF than neurologically intact muscles. Strength training of between 6-8 weeks does not reduce IMF in either partially paralysed muscles of people with SCI or neurologically intact muscles.

DATA ARCHIVING
The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

STATEMENT OF ETHICS
We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

CONFLICT OF INTEREST
The authors declare no conflict of interest.
ACKNOWLEDGEMENTS

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AUTHORS CONTRIBUTIONS

EAB, RDH, JE and JMT came up with the study concept. All authors developed the study design and protocol. EAB and JE collected the study data. All authors, were involved in the analysis and interpretation of data. EAB prepared the first draft of the manuscript. All co-authors provided input and critical review of the manuscript leading to the final version. All authors read and approved the final manuscript.
REFERENCES
Table 1: Characteristics of participants with spinal cord injury (n=10) and neurologically intact participants (n=11).

<table>
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<tr>
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<tr>
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Figure 1: Fraction of intramuscular fat of participants with spinal cord injury (SCI, left column) and able-bodied individuals (right column) before and after training. Bars and error bars are means and standard deviations. Data from individual participants with SCI are shown with participant-specific symbols. All able-bodied individuals are shown with closed triangles. Abbreviations: KE, knee extensors, KF, knee flexors, EF, elbow flexors
Figure 2: Fat fraction (%) versus age (years) for able-bodied individuals and participants with spinal cord injury. Closed circles represent the participants with spinal cord injury and open circles represent the able-bodied individuals. The dotted lines represent the prediction interval: mean ± 1.96SD for the control subjects. The first number next to the closed circle represents time since injury (years) and the second number is initial muscle grade measured on a 13-point scale.

This study has been published. It is presented here in the Author Accepted Version format.


Conference proceedings

This study has been presented at two conferences. It appears in the conference proceedings as:


The inter-rater reliability of the 13-point Manual Muscle Test in people with spinal cord injury.

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Abstract

Study Design: A clinimetric study.
**Objective:** To determine the inter-rater reliability of the 13-point manual muscle test (MMT) in two upper limb muscle groups of people with tetraplegia.

**Setting:** The study was conducted at three spinal cord injury (SCI) units.

**Participants:** Sixty people with complete or incomplete tetraplegia.

**Methods:** The inter-rater reliability of the 13-point MMT was investigated. Strength of the elbow flexors and/or wrist extensors in people with tetraplegia was measured by two physiotherapists on the same day.

**Results:** The weighted kappa coefficient (95% confidence interval) reflecting the agreement between the two strength assessments by two different assessors for the wrist extensors and elbow flexors were 0.96 (0.93 to 0.99) and 0.94 (0.89 to 0.99), respectively. Repeat measurements by different physiotherapists were within 1 of 13 points of each other 82% of the time for wrist extensors and 87% of the time for the elbow flexors.

**Conclusion:** The 13-point MMT is a reliable measure of strength in the wrist extensors and elbow flexors of people with tetraplegia.
INTRODUCTION

Muscle weakness is often a major impairment for people with spinal cord injury (SCI) yet there remains much uncertainty about the effectiveness of different strength-training interventions (Bye et al., 2017, Glinsky et al., 2008, Harvey et al., 2010, Jayaraman, Thompson, Rymer and Hornby, 2013). Consequently, there are increasing numbers of clinical trials designed to investigate this issue. Often these trials examine the effectiveness of interventions in just one muscle group per participant. This is done as a proof-of-concept before embarking on more ambitious trials involving many different muscle groups. However, the use of one muscle group per participant poses a problem if the muscles are very weak, namely, how to easily measure strength in individual muscle groups without the need for expensive or complex equipment.

The most commonly used assessments of strength in clinical trials involving people with SCI are the tallied upper or lower limb motor scores of the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (Kirshblum et al., 2011). These tallied scores have been shown to have good inter-rater and intra-rater reliability (Marino et al., 2008, Savic et al., 2007) and are appropriate in trials where interventions such as treadmill training have an effect on multiple muscle groups, but not for trials targeting individual muscle groups (Bye et al., 2017, Glinsky et al., 2008, Harvey et al., 2010, Jayaraman et al., 2013). A commonly used way to measure strength of individual muscle groups is dynamometry (Riddle, Finucane, Rothstein and Walker, 1989, Sisto and Dyson-Hudson, 2007). However, hand held dynamometers can be problematic for very weak muscles because they require a very sensitive force gauge and careful positioning as small changes in position can influence outcomes. These problems can be minimized with the use of large commercially available dynamometers but they are expensive, not readily
available in clinical practice and not feasible for large multi-centered clinical trials.

Therefore, trialists are increasingly relying on manual muscle testing. The traditional 6-point Medical Research Council (MRC) scale has good reliability (Brandsma et al., 1995, Fan et al., 2010, Lilienfeld, Jacobs and Willis, 1954), but its restricted range limits its sensitivity. We therefore believe it is timely to revisit the 13-point MMT for use in clinical trials, particularly trials in which the muscles are likely to be very weak. Importantly, we are not suggesting that this be used in clinical practice, but instead, only for research purposes.

The 13-point MMT is a modification of the traditional 6-point MRC scale with the addition of “plus” and “minus” scores. There are a number of other variants each with slightly different scales (Barr et al., 1991, Bohannon, 1986, Bohannon, 2001, Florence et al., 1992, Florence et al., 1984, Herbison, Isaac, Cohen and Ditunno, 1996, Kim, Eng and Whittaker, 2004, Paternostro-Sluga et al., 2008, Wadsworth et al., 1987). These were used in SCI clinical trials in the 1990s (Klose et al., 1990, Kohlmeyer, Hill, Yarkony and Jaeger, 1996) but fell out of favor because of concerns about reliability and, in particular, concerns about whether assessors could reliably distinguish between different grades on the scale. However, there is little objective evidence to indicate that these concerns were justified and only a handful of studies have looked at this issue (Barr et al., 1991, Florence et al., 1992, Florence et al., 1984, Paternostro-Sluga et al., 2008, Wadsworth et al., 1987), and none have investigated the reliability of the 13-point MMT in people with SCI.

The merits of using an expanded version of the traditional 6-point MRC scale for clinical trials was recognized by the International Myositis Assessment and Clinical Studies Group (IMACS) who recommend the 0-10 point MMT as a core outcome measure for trials in their area (Miller et al., 2001). The expanded MMT could also be useful to the SCI community in
clinical trials investigating the effects of interventions on individual muscle groups, although we are more interested in the 13-point MMT rather than the 0-10 point MMT because of its increased range. Therefore, the purpose of this study is to test the reliability of the 13-point MMT in two upper limb muscle groups of people with SCI; the elbow flexors and wrist extensors. We chose these two muscles because they are typical of most muscles and can be easily tested in a seated position. They are also important muscles for upper limb function and are thus often the target of clinical trials.

METHODS

The inter-rater reliability of the 13-point MMT was determined for the elbow flexor and wrist extensor muscles of people with tetraplegia. Throughout the paper we refer to points to indicate each increment on the 0-13 point scale. For example, a shift from the equivalent of grade 3 to grade 3+ is a one point shift on the 13-point scale.

Participants

Sixty inpatients and outpatients were recruited from three SCI units (see Table 1 for characteristics of participants) from September 2017 to August 2018. Any newly admitted inpatients or outpatients were screened for eligibility and enrolled if they met the inclusion criteria. The sample size was not based on a formal sample size calculation but instead it was based on the maximal number of people we could realistically recruit within a one-year time frame. Participants were included if they had complete or incomplete tetraplegia as defined by the ISNCSCI, were aged 16 years or over, were willing to participate in the study and were free of any other type of neurological condition or injury. Participants with acute or chronic injuries were recruited regardless of time since injury. Participants were excluded if
they had any condition preventing a strength assessment, were unable to co-operate or if they did not speak English sufficiently well to provide informed consent.

**Procedure**

Muscle strength of the wrist extensors and/or elbow flexors of the left or right side of each participant was assessed by two experienced physiotherapists on the same day consecutively. We allowed a short break between the two assessments of less than five minutes. Strength was measured using the 13-point MMT (see Table 2). All strength assessments were performed in sitting using a standardized procedure. This was as follows; the participant was asked to move his/her limb (either flexing the elbow or extending the wrist) through the available range in a gravity-eliminated position. If the participant could not move through full range, a grade was assigned on the basis of how far through range the participant could move the limb. If the participant could move through full range, he/she was then asked to lift the limb against gravity. Again, a grade was assigned on the basis of how far through range the participant could move the limb. If the participant could lift the limb against gravity through full range, resistance was applied. A grade was assigned on the basis of the amount of resistance applied (see Table 2).

The order of the assessments by physiotherapists was randomized at the time of the assessment, and the assessors were blinded to the results of each other’s assessments. The assessors were instructed and encouraged not to disclose or discuss any part of their assessments during the conduct of the study to maintain blinding of the results. Each assessor underwent training in the use of the 13-point MMT prior to commencement of the study. This involved practicing the assessments together on patients that were not part of the study.
We decided a priori to ensure that our sample included people with an equal spread of strength across the whole 13-point scale. This was to avoid clusters of people with the same strength. We were particularly concerned about clusters of people with no or normal strength where it would be relatively easy to demonstrate good reliability. This would not provide a true reflection of the reliability of the scale. For this reason, we initially tested both the elbow flexors and wrist extensors on one side of the body of all eligible participants. However, towards the end of the recruitment period we became more selective and sometimes only chose one muscle on one side of the body to ensure we had good spread across the range of the scale. These decisions were made prior to testing and were not based on expected reliability.

Data analysis

Data were recorded on paper forms and then transcribed on to the Research Electronic Data Capture (REDCap) Software (Nashville, TN, USA) and analyzed using STATA v13 (Stata-corp, College station, TX, USA). The inter-rater reliability of the 13-point MMT was determined using a weighted kappa (stata code: kap obs1 obs2, wgt(w2) absolute), percent close agreements and Bland-Altman plots. Reliability was determined by comparing the results of the 13-point MMT performed by the two assessors. The Kappa values were interpreted according to a rating system suggested by Landis (Landis and Koch, 1977) (0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial, and 0.81-1.00 almost perfect reliability).

RESULTS

A total of four physiotherapists performed the assessments with one physiotherapist testing the strength of all participants. The median (interquartile range, IQR) years of experience of
the physiotherapists assessing muscle strength was nine years (8.5-17) with a median of five years (3.5-13.5) working in SCI rehabilitation.

The demographic characteristics of the 60 participants are presented in Table 1. The weighted kappa coefficients (95% confidence interval) reflecting the agreement of the two assessors for the wrist extensors and elbow flexors were 0.96 (0.93 to 0.99) and 0.94 (0.89 to 0.99), respectively (see Table 3). The agreement between these two assessments is displayed in the Bland-Altman plot (Figure 1), and the percent close agreements are also shown in Table 3. The two assessors were within one, two and three points of each other (out of 13 points), 82%, 92%, 98%, of the time for the wrist extensors, and 87%, 93% and 100% of the time for the elbow flexors respectively.

**DISCUSSION**

The results of this study indicate that the 13-point MMT has excellent reliability for the wrist extensors and elbow flexors of people with SCI. Notably, the two assessors agreed within one point of each other 82% of the time for the wrist extensors and 87% of the time for the elbow flexors. We only tested reliability in two muscles but nonetheless our results suggest that the 13-point MMT may be a useful outcome measure in clinical trials that investigate the effects of interventions on the strength of isolated muscle groups.

Studies using isolated muscle groups pose a particular problem because composite measures of strength, such as the Upper or Lower Extremity Motor Scores of the ISNCSCI, are not an option. The traditional MRC scale also has limitations because of its restricted range. Similarly, instrumented measures of strength using dynamometers are problematic in this population because they are difficult to use in very weak muscles. The 13-point MMT
overcomes these problems, is quick and easy to administer, and does not require specialized or expensive equipment. This is an important consideration for large multi-centered clinical trials.

Our study is not without its limitations. We only used four assessors, all of whom had extensive experience with the scale and SCI. We therefore do not know about the reliability of the scale when administered by untrained physiotherapists or other healthcare professionals. However, we were primarily interested in the scale for clinical trials where it is appropriate that skilled physiotherapists take the measurements. Similarly, we only tested reliability in two upper limb muscle groups. Future studies will need to verify the reliability of this scale across different muscle groups although we think it is very unlikely that the reliability would be good for one muscle group and not another. We did not assess the validity or sensitivity of the 13-point MMT although we assumed that the 13-point scale would perform as well, if not better than the traditional 6-point MRC scale, in these areas. We initially intended to look at the reliability of the lower end of the scale (grade 3 and less) versus the upper end of the scale (grade 3 and over) however the sample size was not sufficient for these secondary analyses. Future studies could explore this issue further although it will require very large sample sizes because the Kappa statistic is very sensitive to cells (ie., comparisons) with no data.

This study indicates that the 13-point MMT scale has surprisingly good reliability in the wrist extensors and elbow flexors of people with SCI. While these results need replicating in more muscle groups, we believe that they are sufficiently promising to justify its use in clinical trials. We also believe that the SCI community could follow the lead of the IMACS and the Pediatric Rheumatology Clinical Trials Organization (PRINTO) (Oddis, 2005, Ruperto et al.,
2008) and consider using the 13-point MMT as a measure of strength in trials where composite measures of strength are not an option.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest

**ACKNOWLEDGEMENTS**

We would like to thank the participants and physiotherapists who contributed to this study.

**STATEMENT OF ETHICS**

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research. This study was approved by the relevant ethics committees. All participants gave consent to participate.
References


**Table 1 Characteristics of participants.** The neurological levels, ASIA impairment scale classification and motor levels were all defined according to the International Standards for Neurological classification of Spinal Cord Injury

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>55 (35 to 69)</td>
</tr>
<tr>
<td>Sex (F:M), n</td>
<td>12:48</td>
</tr>
<tr>
<td>Time since injury (months), median (IQR)</td>
<td>4 (1.5 to 24)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurological level, n</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-4</td>
<td>32</td>
</tr>
<tr>
<td>C5-8</td>
<td>28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ASIA Impairment Scale classification, n</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>17</td>
</tr>
<tr>
<td>B</td>
<td>14</td>
</tr>
<tr>
<td>C</td>
<td>13</td>
</tr>
<tr>
<td>D</td>
<td>16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Motor level, n</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-4</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>C5-8</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>T1-S5</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 2: 13-point manual muscle test

<table>
<thead>
<tr>
<th>Grades</th>
<th>Points</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>No palpable contraction</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Visible or palpable contraction but unable to move</td>
</tr>
<tr>
<td>1+</td>
<td>2</td>
<td>Able to move through a small range with gravity eliminated</td>
</tr>
<tr>
<td>2-</td>
<td>3</td>
<td>Able to move through a large range with gravity eliminated</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>Able to move through full range with gravity eliminated</td>
</tr>
<tr>
<td>2+</td>
<td>5</td>
<td>Able to move through a small range against gravity</td>
</tr>
<tr>
<td>3-</td>
<td>6</td>
<td>Able to move through a large range against gravity</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>Able to move through full range against gravity</td>
</tr>
<tr>
<td>3+</td>
<td>8</td>
<td>Able to move through a small range with light resistance</td>
</tr>
<tr>
<td>4-</td>
<td>9</td>
<td>Able to move through full range with light resistance</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>Able to move through full range with moderate resistance</td>
</tr>
<tr>
<td>4+</td>
<td>11</td>
<td>Able to move through full range with heavy resistance</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>Normal strength</td>
</tr>
</tbody>
</table>
Table 3: Percent close agreement (cumulative percentages) of the repeat assessments of the 13-point MMT scale for no difference, one point, two point and three point differences, and the weighted kappa coefficients (95% CI) for wrist extensors and elbow flexors

<table>
<thead>
<tr>
<th>Percent close agreement</th>
<th>Wrist extensors</th>
<th>Elbow flexors</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>47%</td>
<td>51%</td>
</tr>
<tr>
<td>1</td>
<td>82%</td>
<td>87%</td>
</tr>
<tr>
<td>2</td>
<td>92%</td>
<td>93%</td>
</tr>
<tr>
<td>3</td>
<td>98%</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weighted kappa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.96 (0.93 to 0.99)</td>
</tr>
<tr>
<td>0.94 (0.89 to 0.99)</td>
</tr>
</tbody>
</table>

Abbreviations: MMT, manual muscle test, CI, confidence interval
Figure 1: Bland-Altman Plot displaying the agreement between the two assessors for each participant. The mean (95% CI) reflecting bias is indicated. The data points have been jittered.
Chapter 6 - Discussion and Conclusion

This chapter is devoted to discussing what I have learnt from the research program, limitations of the studies and directions for future research. I will not repeat the content of the discussions from my publications (Chapter 2, 3, 4 and 5).

The primary objective of this thesis was to investigate the effectiveness of a strengthening program for increasing the strength of partially paralysed muscles in people with SCI. Other objectives were to understand the mechanisms responsible for these strength gains, to investigate the effects of strength training and partial paralysis on fat content of muscles, and finally to assess the reliability of a commonly used strength assessment tool.

Key findings of the research program

There were four key findings of the research program:

• Strength training can increase the strength of partially paralysed muscles of people with recent SCI, although it is unclear whether the size of the treatment effect is clinically meaningful.

• Strength gains in partially paralysed muscles produced by six weeks of strength training are not caused by changes in muscle architecture. Strength gains are therefore probably due to increased neural drive or increases in specific muscle tension.

• A 6- or 8-week strength training program does not change the IMF of partially paralysed muscles following SCI or neurologically intact muscles. Partially paralysed muscles of people with SCI have increased IMF compared to neurologically intact muscles.

• The 13-point MMT has excellent reliability.
Overview of study results

Project One: randomised controlled trial

This RCT was designed to determine whether strength training combined with usual care increases strength in partially paralysed muscles of people with recent SCI more than usual care alone. The results for the primary outcome and secondary outcomes are as below:

- The mean between-group difference (95% CI) for the primary outcome, isometric strength was 4.3Nm (1.9 to 6.8), favouring the intervention group. The minimally worthwhile treatment effect was 2.7Nm.

- Secondary outcomes included perceived change in strength and function, spasticity and resistance to fatigue. Participants were asked to rate their perceived change in strength and function in their trained limb. Their scores indicated they perceived clinically meaningful increases in strength and function. The results indicated that strength training had no deleterious effects on spasticity. The effects of strength training on fatigue were unclear.

Project Two: pretest-posttest study

This pretest-posttest study was designed to investigate mechanisms by which training increases strength of partially paralysed muscles in people with SCI. The results are as below:

- The mean increase in maximal isometric muscle strength was 14% (95% CI, -3% to 30%) and 1.5 points (95% CI, 0.5 to 2.5) on the 13-point MMT. On average, muscle volume increased by 1% (95% CI, -5% to 6%), PCSA decreased by 5% (95% CI, -16% to 6%), mean fascicle length increased by 8% (85% CI, -7% to 24%) and pennation did not change (mean 0%; 95% CI, -12 to 13) in the trained muscle. None of the changes in
architectural measurements were statistically significant; it is reasonable to interpret this as no change.

**Project Three: pretest-posttest study**

This study was a secondary analysis of the data from the above study and another pretest-posttest study on able-bodied individuals. The objective was to compare the amount of intramuscular fat in neurologically intact muscles of able-bodied individuals and partially paralysed muscles of people with SCI, and to determine the effects of a strength-training program on intramuscular fat in the two groups. The results are as below:

- Prior to the training the able-bodied individuals had on average 8% ± 1.9% IMF and the participants with SCI had on average 21% ± 20%.
- In the able-bodied individuals fat content decreased by 0.4% (95% CI, -1.6% to 0.8%).
  In the participants with SCI and partially paralysed muscles, fat content decreased by 0.1% (95% CI, -1.2% to 1%). None of these effects were statistically significant (p > 0.5).

**Project Four: clinimetrics study**

This clinimetric study was designed to determine the inter-rater reliability of the 13-point MMT in two upper limb muscle groups of people with tetraplegia. The results are as below:

- The weighted kappa coefficient (95% CI) displaying the agreement between the two strength assessments for the wrist extensors and elbow flexors were 0.96 (0.93 to 0.99) and 0.94 (0.89 to 0.99), respectively. Repeat measurements by the two physiotherapists were within 1 of 13 points of each other 82% of the time for the wrist extensors and 87% of the time for the biceps.
Partial paralysis is one of the most common impairments that affects people following a SCI. There is a large emphasis on targeting this impairment in rehabilitation programs as it is directly related to a person’s motor function. The RCT described in this thesis provided an unbiased estimate of the effectiveness of progressive resistance training in increasing strength in the partially paralysed muscles of people following SCI.

A key strength of the RCT undertaken during this research program was its design and reporting. The study design included key features aimed at reducing the risk of bias. These included; random and concealed allocation, an independent blinded assessor, intention-to-treat analysis and prospectively registered protocol. In addition, the published manuscript for this RCT was reported in compliance with the reporting guidelines published on the Equator Network website ("Equator Network," titled “Improving the reporting of therapeutic exercise interventions in rehabilitation research” (1, 2).

The concealed randomisation and use of a blinded assessor allowed for good internal validity (3). Blinding of the assessor reduced ascertainment bias (assessment of outcome)(4). The success of blinding was checked by asking the assessor to guess whether the right or left limb was the “trained limb”. The blinded assessor guessed 55% correctly; a result expected by chance indicating that assessors remained blinded over the course of the trial.

Another strength of the RCT was the within-participant study design used to reduce the need for a large sample. This is particularly important in this research area of SCI as it is a small patient population and participants are hard to recruit. The within-participant study design
meant participants acted as their own control. A more precise estimate of treatment effects could be achieved than by using the same sample size in a between-subject design. A much narrower confidence interval therefore was achieved (95% CI, 1.9 to 6.8Nm) than in a previous strength study (95% CI, 1 to 27Nm), which also looked at progressive resistance training in partially paralysed muscles (5).

A strength of the two pretest-posttest studies was the novelty of our measurement technique, DTI. Diffusion tensor imaging has been commonly used to study pathologies of the brain, however its use in studying skeletal muscle is relatively new. Our study was the first to use this technique to study muscle architecture of partially paralysed muscles of people following SCI. This technique could be used to study the effectiveness of other interventions for improving strength of partially paralysed muscles in people with SCI.

The design of our clinimetric study is a strength. All assessors were blinded to the results of the other assessments and the order of the assessments by the physiotherapists was randomised at the time of the assessment. Both of these design features minimised the risk of bias.

**Limitations of research program and its implications for future research**

The limitations of the research program, and its implications and considerations for future research are discussed for each research project separately.

**Project One: randomised controlled trial**

One limitation to our RCT was our failure to blind participants, which threatened internal validity. Unblinded participants may introduce recall bias to their perceptions of change in strength and function; our secondary outcome measure (6). Participants may have been
influenced by their expectations that the strength training was effective. Unfortunately, the inability to blind individuals to the intervention is common in rehabilitation research due to the nature of the interventions. This lack of blinding can introduce bias and tend to exaggerate treatment effects especially with subjective outcome measures (7, 8). We tried to combat this limitation by using an objective primary outcome measure with assessments carried out by a blinded assessor.

Another limitation to our RCT was our fatigue measure. We chose to measure fatigue using a method we have previously used (5, 9). It involves repetitive contractions over a period of 3 minutes (10). We found in this study and in previous studies no improvement in participants’ resistance to fatigue (5, 9). However, we also found that participants were not describing sensations of “fatigue” by the end of the 3 minutes suggesting that maybe our outcome measure was not long enough to induce fatigue in the first place. Another possible explanation was that our training program was not targeting endurance. We know from able bodied literature that a different training protocol is required to train endurance such as lower loads but high repetitions (11). So our failure to detect any fatigue may be due to our training protocol. The other possibility is that partially paralysed muscles do not fatigue like non-paralysed muscles due to the limited available motor units, however future studies would be needed to further explore this idea.

In this RCT, only muscles with Grade 3 and 4 were included. Future studies should examine the effectiveness of strength-training programs in much weaker muscles with Grades 1-3 on MMT. Our study also only included participants who were injured within 1 year. It would be interesting to train participants with more chronic injuries to see if similar gains are made.
Project Two: pretest-posttest study

The main limitation to this study was its design. We chose not to conduct a randomised controlled trial due to the expense of the scans and the exploratory nature of the study. However, without randomisation we cannot rule out the risk of bias, for example the changes in strength may have occurred over time without training. A larger randomised trial would be a more rigorous and appropriate study design.

Recruitment in this patient population can be challenging for large research projects. Therefore, establishing selection criteria can be crucial to recruitment rates. If your selection criteria are tight, your recruitment may be slow, as many people may not fit the criteria. However, if your selection criteria are too broad, your sample may not be homogenous and cannot be generalised to a specific patient population (12). A broad inclusion criteria will mean variability in the sample which may also affect the precision of the estimate of the treatment effect. This may have been the case for our study in which we recruited people with a wide variation in strength deficits. Our inclusion criteria meant participants had strength deficits from 1/5 to 4/5 on the 6-point (0-5) scale. From previous studies it has been shown that very weak muscles (1-2/5 on MMT) respond differently to strength training (9) compared to stronger muscles (3-4/5 on MMT)(13). The heterogeneity of our patient population may have resulted in the large variability in our data and the imprecision of our point estimate (95% -3% to 30%) for our strength assessment.

Future studies should measure neural drive using twitch interpolation techniques to further understand potential mechanisms driving strength gains in partially paralysed muscles. Twitch interpolation has previously been used to compare voluntary muscle strength in people with SCI and able-bodied individuals (14, 15). Twitch interpolation can be used to measure
voluntary “activation” of muscles. It has not been used yet to study improvements in “activation” following a period of progressive resistance training in partially paralysed muscles. This study would help us understand if neural drive is an important mechanism leading to strength gains in these muscles and whether interventions should be targeting improvements in neural drive such as motor imagery or electrical stimulation (16). A longer training period could also be used to investigate whether muscle architectural changes occur with a greater training stimulus.

**Project Three: pretest-posttest studies**

There are several limitations to our analysis of the two pretest-posttest studies. Firstly, we compared the proportion of IMF in neurologically intact muscles of adults with partially paralysed muscles of people with SCI, however the people with SCI were on average 22 years older than our able-bodied controls. Therefore, it is difficult to say if the differences in IMF proportions were as a consequence of SCI or age. However, even if the two groups were aged matched both groups are very small samples of convenience, making it very difficult to generalise the results to a larger population.

Secondly, while mDixon scans have been shown to be valid (17-19), repeatable (20) and reproducible(21), we did not formally test this for the participants with SCI. We did repeat the baseline scans for four of our neurologically intact participants, however this would need to be further tested on a larger population and in participants with SCI.

Future studies could examine the effects of progressive resistance training plus electrical stimulation in partially paralysed muscles to reduce IMF. As outlined in the literature review, there are a number of studies that have examined the effects of electrical stimulation on
reducing IMF in completely paralysed muscles (22-24). Potentially, the added stimulus from the electrical stimulation may provide a larger drive to the muscle leading to improved structural changes.

**Project Four: clinimetrics study**

Although this study demonstrated excellent inter-rater reliability for the 13-point MMT scale in people with SCI for elbow flexors and wrist extensors, there are still questions about other aspects of the scale. For example, we only tested the reliability of two muscle groups; elbow flexors and wrist extensors. Future studies would need to test the reliability in a range of muscle groups. We also did not test the intra-rater reliability of the scale which would be worthwhile considering it is preferable for the same assessor to perform baseline and follow-up assessments in a clinical trial.

To avoid excessive representation of the two extremes of the scale we decided to stop recruiting people at the extremes of the range once they were well represented. This decision was made after careful consideration in order to avoid inflating our estimates.

Future studies could examine the inter- and intra-rater reliability of the 13-point scale using less experienced clinicians who do not work in the area of SCI rehabilitation or other health professions such as occupational therapists or physiotherapy students who may be involved with data collection for studies. Other studies should also examine its reliability in a wider range of muscles.
Summary

Previously, very little was known about the responsiveness of partially paralysed muscles following SCI to progressive resistance training. This thesis describes the body of evidence to suggest that progressive resistance training is effective in strengthening partially paralysed muscles. The randomised controlled trial described in this thesis demonstrates this but leaves the question as to how clinically meaningful these gains are.

The second study examined the mechanisms responsible for the strength gains of partially paralysed muscles following a 6-week strength training program. This was the first study to observe muscle architectural changes in partially paralysed muscles following SCI. The study was exploratory in nature and therefore had a small sample size. The results indicated no evidence of a systematic change in muscle architecture suggesting other mechanisms may be responsible for the strength gains but further studies are required to further explore this idea.

Our study showed no changes in IMF in partially paralysed muscles or in neurologically intact muscles following a strength-training program. This finding is in contrast to some previous studies (25-27), which may reflect our small sample size and shorter training period. These studies also used different methods to measure IMF, namely CT and T1-weighted imaging.

Lastly, in all of these studies and any study examining the effects of a strengthening intervention on maximal strength, a reliable outcome measure is needed. Our clinimetric study demonstrated that the 13-point MMT scale, an expanded version of the traditional 6-point MRC scale, has excellent reliability and may be an appropriate outcome measure in clinical trials.
Strength training is an integral part of any rehabilitation program following a SCI. As we have seen both anecdotally and in the research, (28) physiotherapists dedicate large amounts of time to strengthening programs. The findings from the RCT provide some of the first evidence to suggest that progressive resistance training is effective for strengthening partially paralysed muscles with Grade 3 and 4 on MMT, however it is still unclear how clinically meaningful these results are. In light of these results and from previous results in the area (5, 9) the use of strength training should be advocated for strengthening stronger muscles (Grade 3 and above). However, we are less confident about what to advocate for people with weaker muscles (less than Grade 3) until our results have been independently confirmed, and until other interventions have been tested. In addition, the underlying mechanisms driving these strength gains are not clear nor do we have evidence to suggest this type of training can reduce IMF. Lastly, the 13-point MMT scale may be a reliable measurement tool useful for measuring the effectiveness of interventions targeted at increasing the strength of very weak muscles.
Reference list

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