Strengthening interventions for people after stroke

Davide Gabriel de Sousa
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Sydney Medical School - Northern
The University of Sydney

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Candidate's statement

I, Davide Gabriel de Sousa, hereby declare that this submission is my own work and that it does not contain material that has been accepted for the award of another degree.

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Supervisors' statement

As supervisor of Davide Gabriel de Sousa's doctoral work, I certify that I consider this thesis "Strengthening interventions for people after stroke" to be suitable for examination.

Professor Lisa Anne Harvey, Primary Supervisor, John Walsh Centre for Rehabilitation Research, Faculty of Medicine, The University of Sydney.

Signed Date: 30-Aug-2019

Dr Simone Dorsch, Secondary Supervisor, Faculty of Health Sciences, Australian Catholic University.

Signed Date: 30-Aug-2019

Abstract

Stroke is one of the leading causes of death and disability. Muscle weakness (or loss of voluntary muscle strength) in the paretic arm and leg is one of the most common impairments after stroke. Muscle weakness has been identified as one of the main contributors to activity limitations (such as walking or reaching and manipulation) and participation restrictions. Many people who are very weak and immobile after stroke have few options for exercising independently and few studies have specifically investigated this issue. Many people after stroke also have difficulty standing up due to weakness and poor coordination. The inability to stand up can be very disabling and can lead to increased burden of care. Again, few studies have specifically investigated this issue in people who are very weak and immobile.

This thesis includes a systematic review that investigated the effects of commonly-used interventions to improve strength and activity after stroke. This thesis also includes a randomised controlled trial investigating the effects of providing a strengthening intervention (Functional Electrical Stimulation cycling) that can provide more opportunities for people who are very weak and immobile after acquired brain injury to exercise independently, and a randomised controlled trial investigating if intensive sit-to-stand training improves lower limb strength and the ability to stand up in people who are unable to stand up independently after stroke.

Study one was a systematic review of 52 randomised controlled trials with meta-analysis, investigating if interventions involving repetitive practice improve strength after stroke, and if any improvements in strength are accompanied by improvements in activity. Forty-six studies with a total of 1928 participants investigated the effects of repetitive practice on strength. The

overall SMD of repetitive practice on strength when the upper and lower limb studies were combined was 0.25 SD (95% CI 0.16 to 0.34, $I^2 = 44\%$) in favour of repetitive practice. These results indicate that interventions involving repetitive practice *do* improve strength after stroke, and improvements in strength *are* accompanied by improvements in activity.

Study two was an assessor-blinded, multi-centre randomised controlled trial investigating the effects of Functional Electrical Stimulation (FES) cycling on mobility and strength after acquired brain injury caused by stroke or trauma. Forty patients from three hospitals with recently acquired brain injury were randomised to an experimental group which received four weeks of FES cycling in addition to usual care, or a control group which received usual care only. The mean between-group differences (95% CI) for mobility and strength of the knee extensors of the paretic lower limb were –0.3/21 points (–3.2 to 2.7) and 7.5 Nm (–5.1 to 20.2), respectively, where positive values favoured the experimental group. These results indicate that FES cycling does not improve mobility in people with acquired brain injury and its effects on strength are unclear.

Study three was an assessor-blinded, multi-centre randomised controlled trial investigating the effects of intensive sit-to-stand training on sit-to-stand ability and gross lower limb extension strength in people who are unable to stand up independently after stroke. Thirty patients from two hospitals, less than three months after stroke were randomised to an experimental group which received two weeks of intensive sit-to-stand training in addition to usual care, or a control group which received usual care only. The mean between-group differences (95% CI) for clinicians' impressions of sit-to-stand change and gross lower limb extension strength were 1.57/15 points (0.02 to 3.11) and 6.2 degrees (0.5 to 11.9), respectively. These results indicate that two weeks of intensive sit-to-stand training in addition to usual care improves sit-to-stand

ability and gross lower limb extension strength in people who are unable to stand up independently after stroke.

The results from this research program suggest that:

1. Interventions involving repetitive practice should be prioritised in stroke rehabilitation programs because these interventions can improve both strength and activity after stroke.
2. Functional Electrical Stimulation cycling in addition to usual care may provide more opportunities for people who are very weak and immobile after acquired brain injury caused by stroke or trauma to improve lower limb strength, but there are no accompanied improvements in mobility.
3. Intensive sit-to-stand training in addition to usual care improves sit-to-stand ability and gross lower limb extension strength in people who are unable to stand up independently after stroke.

More clinical trials are needed to better understand the effects of different amounts of strengthening interventions that promote repetitive practice for different tasks, and in different subgroups of people after stroke (i.e. weak versus very weak).

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To the participants of this research program and to all people affected by stroke. I acknowledge your challenges and stand with you to regain your independence. This research is for you.

Contents

Chapter 1 Introduction

Background and rationale

Muscle weakness (or loss of voluntary muscle strength) after stroke is a common and important impairment. Some studies estimate a loss of 50 to 70% strength in the paretic upper and lower limbs when compared to aged-matched controls [1-4]. This loss of strength has been identified as one of the main contributors to activity limitations [5-7] (such as limitations in walking or reaching and manipulation) and participation restrictions [8] after stroke.

To regain the ability to use the paretic upper and lower limbs, people after stroke participate in repetitive practice of tasks such as walking or reaching and manipulation [9]. This repetitive practice is a major component of rehabilitation after stroke [10]. Some interventions used to promote repetitive practice include constraint-induced movement therapy, body weight supported treadmill walking, or robotic devices. There are systematic reviews [11-14] supporting the use of these interventions to improve *activity* of the paretic upper and lower limbs, however, less is known about the effects of repetitive practice on *strength* after stroke and no systematic reviews have specifically investigated this issue.

Therefore, the aim of study one (a systematic review) was to determine if interventions involving repetitive practice improve strength after stroke, and if any improvements in strength are accompanied by improvements in activity.

Whilst it is known that repetitive practice of walking in combination with strengthening interventions improves walking [9], many people after stroke never regain the ability to walk. One estimate indicates that 40% of people after stroke who are unable to walk on admission to

rehabilitation are still unable to walk at three months [15]. One reason for this could be because many patients who are very weak and immobile after stroke have few options for exercising independently and often require assistance from one or more physiotherapists, which is costly and time consuming. These patients often remain inactive for as much as 70% of the day [16-18] and have less opportunities to improve their lower limb strength, which is a major determinant of walking. Systematic reviews indicate that FES improves upper and lower limb strength and activity [19 20]. However, these reviews did not include trials investigating the effects of FES cycling. There are also very few randomised controlled trials investigating the effects of FES cycling on lower limb strength and mobility in people after stroke. The two trials that do exist have not conclusively answered this question, that is, one showed improvements in lower limb strength but not mobility [21], and the other showed improvements in mobility but not lower limb strength [22]. Additionally, few studies have specifically investigated ways of providing more opportunities for people who are very weak and immobile to exercise independently.

Therefore, the aim of study two (a randomised controlled trial) was to determine if four weeks FES cycling in addition to usual care improves mobility and strength in people with a sub-acute acquired brain injury caused by stroke or trauma. Functional Electrical Stimulation cycling is appealing to physiotherapists because it is a relatively inexpensive intervention that does not require direct assistance. Functional Electrical Stimulation cycling also allows people who are very weak and immobile after stroke to perform a strengthening intervention independently while physiotherapists assist other patients with their rehabilitation programs.

After stroke, many people have difficulty standing up due to weakness and poor coordination. The inability to stand up can be very disabling [23] and can lead to increased burden of care

[24]. There is some indication from systematic reviews that large amounts of repetitive practice improves functional outcomes after stroke [25-28]. However, there are very few randomised controlled trials investigating if large amounts of repetitive sit-to-stand training is effective in people after stroke. Trials investigating the effects of additional sit-to-stand training have not conclusively answered this question, because they recruited people who can already stand up independently [29-32] or had methodological issues affecting the validity of the results [33]. Furthermore, people in the early stages of rehabilitation after stroke may not be able to tolerate large amounts of repetitive sit-to-stand training and this has not been investigated.

Therefore, the aim of study three (a randomised controlled trial) was to determine if intensive sit-to-stand training in addition to usual care improves sit-to-stand ability in people who are unable to stand up independently after stroke. Secondary aims were to determine if large amounts of sit-to-stand training are well tolerated in the early stages of stroke recovery, and if any improvements in sit-to-stand are accompanied by improvements in lower limb strength.

In summary, the primary objectives of this research program were:

1. To determine if interventions involving repetitive practice improve strength after stroke, and if any improvements in strength are accompanied by improvements in activity.
2. To determine if four weeks FES cycling in addition to usual care improves mobility and strength in people with a sub-acute acquired brain injury caused by stroke or trauma.
3. To determine if intensive sit-to-stand training in addition to usual care improves sit-to-stand ability and gross lower limb extension strength in people who are very weak and immobile after stroke.

Outline of thesis

This thesis consists of six chapters.

Chapter 1

Background and rationale for this research program.

Chapter 2

A critical review of the literature relating to the loss of strength after stroke and interventions that improve strength and activity.

Chapter 3

A systematic review

Project title: *Interventions involving repetitive practice improve strength after stroke: a systematic review.*

Chapter 4

A randomised controlled trial

Project title: *Functional electrical stimulation cycling does not improve mobility in people with acquired brain injury and its effects on strength are unclear: a randomised trial.*

Chapter 5

A randomised controlled trial

Project title: *Two weeks of intensive sit-to-stand training in addition to usual care improves sit-to-stand in people who are unable to stand up independently after stroke: a randomised trial*

Chapter 6

A summary of the primary objectives and key findings of this research program and an overview of each study conducted in this research program including results, strengths, limitations and implications for future research.

Chapter 2 Literature Review

Overview of acquired brain injury

Acquired brain injury (ABI) refers to any damage to the brain that occurs after birth. This damage can be caused by stroke, trauma, infection, cancer, alcohol, drugs, or diseases affecting the brain like Parkinson's disease and Multiple Sclerosis [34]. It is estimated that over 700,000 Australians are living with ABI with three out of every four aged under 65 years and male [34].

Stroke is the leading cause of ABI and disability in Australia [34 35]. Approximately 56,000 strokes occur each year in Australia, equating to over 1,000 strokes every week or one every 9 minutes [35]. Globally, stroke is the highest contributor of neurological disability-adjusted life years (DALYs: the sum of years of life lost and years lived with disability) (42.2% [38.6–46.1])[36] and the second leading cause of DALYs [37].

As much as 65% of people following stroke have a disability that prevents them from carrying out daily living activities unassisted [35]. Activity limitation following stroke leads to participation restrictions and may impact on quality of life.

Classification of stroke

Strokes can be classified into two major categories: Ischaemic and Haemorrhagic. Both categories of stroke cause disruption of blood supply to the brain resulting in death to brain cells in the area of the infarct. This cell death commonly results in weakness and other impairments on the contralateral side of the body [38].

Ischaemic strokes are caused by interruption of the blood supply to the brain through four mechanisms:

1. Thrombosis (obstruction of a blood vessel by a blood clot forming locally)
2. Embolism (obstruction of a blood vessel by an embolus formed elsewhere in the body)
3. Systemic hypo-perfusion (systemic decrease in blood supply)
4. Cerebral venous sinus thrombosis (blood clot in the cerebral veins or sinuses)

Ischaemic strokes account for approximately 80% of all stroke episodes [38]. There are various classification systems for ischaemic stroke. The Bamford (or Oxford) classification system is commonly used and categorises stroke based on initial presenting symptoms and clinical signs [39]. A classification of stroke is assigned to people based on the findings of a clinical neurological examination and a brain computed tomography scan. The following classifications are assigned to people:

- **Lacunar infarcts (LACI)** - A subcortical stroke (i.e. involving the basal ganglia or pons) occurring secondary to small vessel occlusion. Symptoms need to include one of the following:
    - Pure sensory impairment
    - Pure motor impairment
    - Sensory-motor impairment
    - Ataxia
- **Total anterior circulation infarcts (TACI)** – A cortical stroke affecting areas of the brain supplied by both the middle and anterior cerebral arteries. Symptoms need to include all three of the following:
    - Unilateral weakness (and/or sensory impairment) of the face, arm and leg
    - Homonymous hemianopia

    - Higher cerebral dysfunction (i.e. dysphasia or visuospatial disorder)

- **Partial anterior circulation infarcts (PACI)** – A cortical stroke affecting areas of the brain supplied by the anterior cerebral artery. Symptoms need to include two of the following:
    - Unilateral weakness (and/or sensory impairment) of the face, arm and leg
    - Homonymous hemianopia
    - Higher cerebral dysfunction (i.e. dysphasia or visuospatial disorder)
- **Posterior circulation infarcts (POCI)** – A stroke affecting areas of the brain supplied by the posterior cerebral artery. Symptoms need to include one of the following:
    - Cranial nerve palsy and contralateral motor sensory impairment
    - Bilateral motor/sensory impairment
    - Conjugate eye movement disorder
    - Cerebellar dysfunction (i.e. ataxia, nystagmus, vertigo)
    - Isolated homonymous hemianopia

Haemorrhagic strokes account for the remaining 20% of all stroke episodes and are most commonly caused by rupture of small aneurysms. These aneurysms are commonly caused by hypertensive small-vessel disease [40]. Other causes of aneurysms are from intracranial vascular malformations, cerebral amyloid angiopathy, or infarcts into which secondary haemorrhages have occurred [38]. Haemorrhages are divided into two sub-types: Intracerebral (bleeding that occurs within the brain) and subarachnoid (bleeding that occurs outside the brain tissue, between the pia mater and arachnoid mater). An intracerebral haemorrhage can occur within the brain tissue (intraparenchymal) or within the ventricles (intraventricular) [40].

Rehabilitation after stroke

In Australia, people after stroke are admitted to an acute hospital where they are medically stabilised and a confirmed medical diagnosis (using brain imaging and physical assessment) is provided. Further medical investigations and interventions such as thrombolysis or endovascular clot retrieval may be administered, provided these interventions are performed within a few hours after stroke. The gold standard for acute stroke care has been well established through research, and it is recommended that all people after stroke be cared for by a specialised team of health professionals in a stroke unit [41]. Once they have been medically stabilised in a stroke unit, some patients who have had a less severe stroke may be discharged home (ideally with involvement from a community team of health professionals), and other patients who have had a moderate to severe stroke will be transferred to a sub-acute rehabilitation unit for ongoing rehabilitation. The broad aims of rehabilitation after stroke are to provide the following: a multidisciplinary assessment of the person's sensorimotor impairments, activity limitations and participation restrictions; goal setting with patients and carers; provision of an intensive multidisciplinary rehabilitation program through one-to-one and/or group therapy (in line with evidence-based guidelines for best practice); education and training to patients and carers regarding self-management strategies and re-integration into the community. The rehabilitation program should be patient-centred and designed to assist patients achieve short and long-term participation goals [42].

The multidisciplinary rehabilitation team in Australia usually includes physiotherapists. Physiotherapists assess and treat people with sensorimotor impairments and activity limitations caused by stroke. To maximise physical recovery, it is recommended that people after stroke participate in an intensive program of task-specific training which addresses activity limitations

[10]. However, many people after stroke cannot perform task-specific training due to profound muscle weakness, and therefore require interventions to improve strength prior to, or in combination with task-specific training. Physiotherapists typically provide these strengthening interventions aimed at restoring movement to weak limbs in combination with repetitive practice of tasks, such as standing up, walking, and reaching and manipulation.

Weakness after stroke

Weakness after stroke can be attributed to neural and muscular changes. The following sections will briefly discuss the causes of weakness, the neural and muscular changes associated with weakness, and the distribution of muscle weakness after stroke.

Neural changes

Neural changes after stroke are a consequence of the damage to upper motor neurones, following ischaemia in the brain. The damage to the upper motor neurones reduces excitability of lower motor neurones, which in turn, prevents the high frequency neural impulses required to produce tetanic muscle contractions that are needed to produce sufficient force to move a limb [43]. This has been called voluntary activation failure and has been observed in both the paretic and non-paretic limbs; however, voluntary activation failure is greater in the paretic limb/s after stroke [44 45]. As a consequence of voluntary activation failure, a significant amount of lower motor neurones innervating the paretic upper and lower limbs cease to function [46]. Voluntary activation failure has been observed to remain unchanged over six months, in a small sample of people after stroke [45]. Other neural changes include changes in order of motor unit recruitment and changes in firing rates of motor units [47-49]. For example, a loss of 37% [46] and 38% [50] of the motor units of the extensor digitorum brevis and

abductor pollicis brevis (respectively) on the paretic side have been observed in the first 2 to 6 months after stroke.

Muscular changes

Muscular changes after stroke can be a consequence of denervation of the motor units causing morphological and mechanical changes to muscle tissue [51]. For example, some studies have reported changes in lean muscle mass of the paretic lower limb as early as three weeks [52] and two months [53] after stroke. However, there is conflicting evidence from other studies that have not reported similar results [54]. A systematic review of studies with people at least 6 months after stroke helped to clarified this issue by providing estimates for lean muscle mass and cross-sectional area of muscles in the paretic upper and lower limbs [55]. This review found that there was 249g (95% CI 182 to 298) and 342g (95% CI 247 to 438) less lean muscle mass in the paretic upper and lower limbs, respectively, when compared to the non-paretic limbs [55]. There was also less cross-sectional area of the mid-thigh in the paretic lower limb when compared to the non-paretic lower limb (MD 15cm^2, 95% CI 14 to 17). A similar estimate of 20% less cross-sectional area of the mid-thigh in the paretic lower limb (compared to the non-paretic lower limb) was found in a more recent study of a small cohort (n = 16) of people in the late stages of stroke recovery [56]. This study also found that intramuscular fat was much higher in the paretic lower limb when compared to the non-paretic lower limb.

Another suggested cause for loss of muscle mass in people after stroke is the presence of spasticity [46 57]. The presence of spasticity can result in muscles remaining in a shortened position leading to soft tissue plastic changes, i.e. progressive loss of sarcomeres and contracture [58 59]. Muscle contracture resulting from these soft tissue plastic changes has been

proposed to further aggravate spasticity, thus perpetuating the cycle of immobilisation, contracture, and spasticity [60].

Decreased activity and disuse are also contributors to loss of muscle mass (atrophy) and weakness after stroke [61 62]. Muscle atrophy has been described as a decrease in muscle protein content and muscle fibre diameter, which in turn reduces force production and fatigue resistance of the muscle fibres [63].

Distribution of muscle weakness

Historically it was assumed that distal muscle groups of the paretic upper and lower limbs were weaker than proximal after stroke (i.e. wrist extensors were weaker than shoulder abductors). This assumption was based on early studies investigating the distribution of muscle weakness [64 65]. However, since then, several studies have reported contradictory results, that is, either proximal muscle groups of the paretic upper and lower limbs were weaker than distal muscle groups [2 3], or there were no statistical differences between the proximal and distal muscle groups of the paretic limb [66 67]. The reasons for these contradictory results could be due to earlier studies recruiting small, non-representative samples or due to investigators not measuring the strength of all muscle groups in the paretic limb [66].

Relation between strength and activity

The relation between strength and activity has been investigated in older people without disability with an apparent association between the two. Buchner et al investigated this association in a large cross-sectional study (n = 409) of community dwelling older people (age = 60 to 90 years) without muscular pathology [68]. These investigators found that age-related loss of strength explained 17 – 22% of the decline in walking speed. Buchner et al also identified a curvilinear relationship between lower limb strength and walking speed, and

hypothesised that changes in strength have associated effects on activity in weaker adults; however, changes in strength have little or no effect on activity in stronger adults [68]. This curvilinear relationship can be seen in Figure 1 below. Area A represents no association between strength and walking speed as typically seen in strong young adults. Area B represents a strong association between strength and walking speed with small changes in strength resulting in large changes in walking speed. This is what is typically seen in weaker and older adults. Area C represents profound weakness that prevents walking as typically seen in adults after stroke or older adults that are extremely weak.

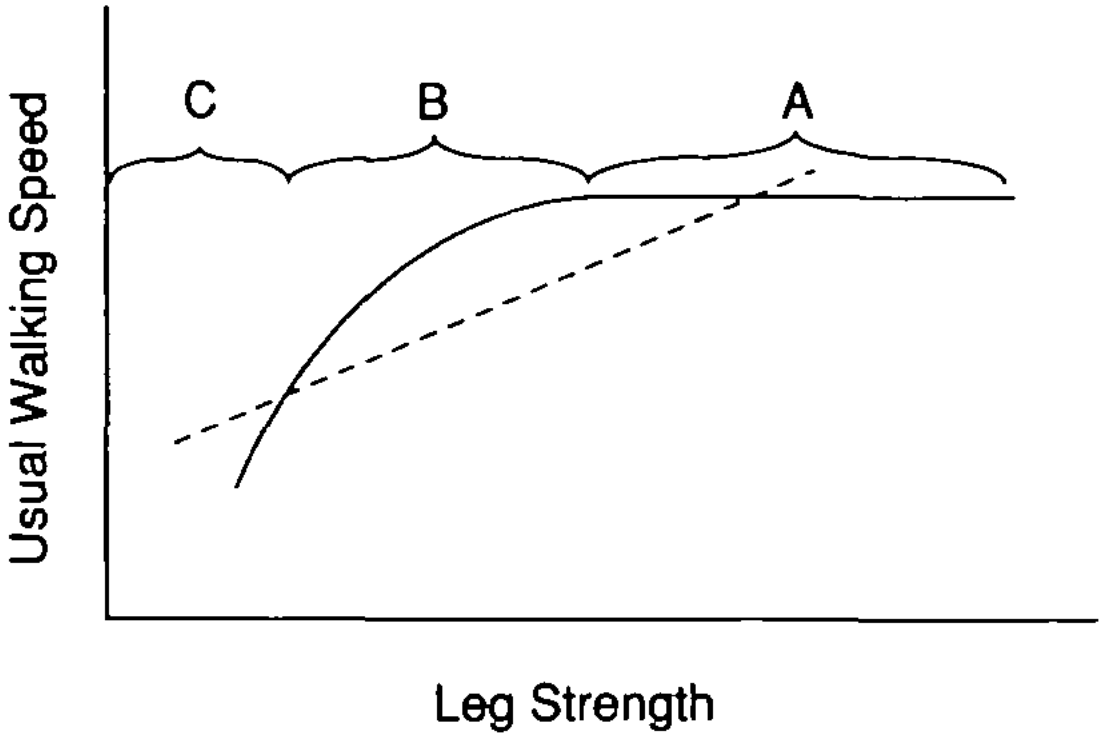

Figure 1. Hypothesized relationship between lower limb strength and walking speed. (Buchner et al, 1996)

In people after stroke with muscle weakness, it is reasonable to assume the association between strength and activity is larger than in older people without disability. A narrative review identified more than 50 studies with significant correlations between strength and activity after stroke [69]. Some of the studies included in this review found correlation co-efficients as high

as 0.85 [70-72]. However, all of these studies measured strength in different combinations of muscles and no study measured strength in *all* muscles of the upper or lower limb [73]. This may be an issue when prioritising which muscles to strengthen after stroke because different tasks will require different amounts of strength from the same muscle group. For example, walking may require less strength in the knee extensors than standing up [74-76]. Dorsch et al measured strength all main muscle groups in the paretic lower limb of 60 people, one to six years after stroke [73]. These investigators found that the ankle dorsiflexors accounted for 31% of the variance in walking speed [73]. Another observational study of similar size found comparable results between dorsiflexor strength and walking speed (r = 0.50 – 0.73) [77], suggesting there is a moderate correlation between lower limb strength and activity after stroke. Similar correlations between upper limb strength and activity have also been observed (r = 0.71 – 0.88) in other studies [78-80]. Faria-Fortini et al investigated the association between upper limb strength and activity in 55 community dwelling people, at least 6 months after stroke. This study found moderate to high correlations between hand-grip and lateral pinch strength, and activity (r = 0.50 – 0.82) [7].

These studies all suggest a moderate to strong relationship between the loss of strength and activity. However, many observational studies investigating the relationship between strength and activity are small, recruited samples of convenience, and do not measure strength in all muscle groups of the paretic limb being investigated. Therefore, these studies need to be interpreted with caution as they may not be representative of the population of people after stroke. More importantly, there may be confounding factors explaining the observed relationship between strength and activity that have not been controlled for in many observational studies.

In summary, studies in older people and people after stroke have concluded that there is a clear relationship between strength and activity. However, this relationship may not be as simple as depicted in Figure 1, because there may be possible confounders that were not considered in these studies. The findings of these studies do provide interim data that should be further explored in well-designed observational studies using more complex modelling that considers confounders. In absence of these data, the results of the reviewed studies have implications for people who are weak after stroke, because muscle weakness may lead to activity limitations and participation restrictions, which in turn, may lead to reduced quality of life. It is therefore important that people after stroke participate in strengthening interventions in rehabilitation programs, in conjunction with interventions that focus on improving activity.

Measurement of strength

There are a several ways to measure muscle strength ranging from simple methods involving no equipment to methods involving complex machinery. This section will define and discuss the two methods of strength measurement used in the clinical trials (studies two and three) associated with this research program: hand-held dynamometry and manual muscle testing. There will also be a discussion about why these strength measures were used and the different issues encountered whilst using these measures in this research program.

Hand-held dynamometry

Hand-held dynamometry involves using a portable device that measures force. Two types of tests can be used to measure muscle force: *Break tests* or *Make tests*. *Break tests* require the examiner to push against the subject's limb until the subject's maximal muscular effort is overcome and the limb gives way [81]. *Make tests* involve the examiner holding the dynamometer against the limb while the subject exerts maximal force against it [81]. In both

tests, torque is then calculated by multiplying the force by the perpendicular distance between the axis of rotation and the place at which force is measured. Torque is expressed in Newton Meters (Nm).

Hand-held dynamometry has been shown to have "very good" inter-rater reliability with patients in the rehabilitation setting [82], as well as "very good" intra-rater reliability for measurements of strength in patients with neurological conditions [83]. *Make* and *Break* tests have been tested for reliability in the elbow flexors and although *Break tests* were associated with higher force production, both tests were considered reliable, provided the examiner had sufficient strength to match the strength of the participant [81]. Wikholm and Bohannon (1991) found that the strength of the examiner affected the inter-rater reliability of hand-held dynamometry [84], therefore, a *Make test* was used in study two to improve inter-rater reliability with multiple assessors.

Manual Muscle Testing

Manual muscle testing is the most widely used method of measuring muscle strength in the clinical setting. Clinicians assign a score ranging from zero to five, where zero represents no muscle activation and five represents normal muscle strength [85]. Grades zero to three are examined in relation to the force of gravity acting against the limb, whereas, grades four and five are examined in relation to force applied to the limb by the tester [85]. One of the criticisms of manual muscle testing is its poor sensitivity to detect differences in muscle strength at grades four and five [86]. This is because grades four and five encompass a large range of possible strength measurements [87] and the amount of resistance provided by the tester for grades four and five can be variable and hard to quantify [88 89]. For this reason, the strength considered a grade five (normal strength) could be substantially lower when compared to normal strength

for that muscle group [86]. Despite this issue, the inter- and intra-rater reliability of manual muscle testing has shown to be mostly "very good" in a group of older individuals following stroke [90]. These investigators used a strict protocol for measurement in their study, which improves reliability; however, in clinical practice there are sometimes great differences between clinicians when performing manual muscle testing. Therefore, manual muscle testing may not be the most reliable method of testing muscle strength in clinical practice.

Hand-held dynamometry and manual muscle testing were used in studies two and three of this research program due to ease of use in a clinical setting. However, given the limitations of manual muscle testing it was used as a secondary outcome measure to explore possible mechanisms underlying the observed effects of the interventions on activity. In an attempt to improve intra- and inter-rater reliability of these measurements of strength a strict protocol was used in the two studies [85]. For example, to improve the intra- and inter-rater reliability of hand-held dynamometry with multiple assessors, a *Make test* was used in study two. Assessments were standardised by ensuring that participants were positioned in the same way for baseline and follow-up assessments. Assessors were positioned so that the dynamometer would remain still when force was applied by the participant. In study two it was identified that manual muscle testing is not sensitive enough to use as a screening tool to detect neurological weakness. Since one of the inclusion criteria for study two was hemiparesis (i.e. ≤ grade 4), some patients may have been incorrectly classified as grade 5 and hence excluded from participation in the study when in fact they were grade 4. This is because, patients may have presented with neurological weakness that was undetectable with manual muscle testing alone. Furthermore, screening was performed over three hospital sites with multiple staff, and there may have been much inter-rater variability when conducting the screening. However, it would

have been too time-consuming to use hand-held dynamometry when screening patients on a daily basis and training many staff over multiple sites was not feasible.

Management of weakness after stroke

This section will discuss five strengthening interventions to manage weakness after stroke. This is not an exhaustive list and only includes interventions most commonly used in stroke rehabilitation. Progressive Resistance Training (PRT) will be discussed as one of the five interventions and although PRT is not commonly used in stroke rehabilitation it is considered to be the most effective strengthening intervention for people without disability. For each intervention there will be a review and discussion of the studies investigating the effects of that intervention on *strength* and *activity*.

Studies that have reported effect sizes using SMD will be interpreted using Cohen's interpretation of effect size, i.e. effect size values of 0.00 to ≤0.49 indicate a small effect size, values of 0.50 to ≤0.79 indicate a medium effect size and values ≥0.80 indicate large effect sizes [91].

Electrical Stimulation

Electrical stimulation (ES) is the application of an electrical current, usually via electrodes placed on the skin. Electrical stimulation can be broadly divided into two types based on whether the stimulation targets sensory neurones only, or both sensory and motor neurones to elicit a muscle contraction. The strength of the sensory stimulus and/or muscle contraction depends on the number of neurones stimulated, and also on the frequency, pulse width and intensity of the current [92]. There are many names given to ES, however, there is no consistency in the literature regarding the use of these names. Therefore, ES that only targets

sensory neurones will be called Transcutaneous Electrical Neuromuscular Stimulation and will not be discussed in this thesis. Electrical stimulation that targets both sensory and motor neurones will be called ES.

Electrical stimulation has been further divided into two categories: cyclical ES and Functional Electrical Stimulation (FES) [93]. Cyclical ES involves repeated electrical stimulation of an isolated muscle (or muscle group) at maximally tolerated levels of contraction, with the primary aim of strengthening that muscle [20]. Functional Electrical Stimulation involves electrical stimulation of a muscle (or several muscle groups) during the performance of an activity, with the primary aim of improving performance of that activity [94]. It is important to note that people can remain passive (i.e. not contract their muscles in synchrony with ES) with both cyclical ES and FES, because it is difficult to know if a person is consciously attempting to contract their muscles. However, it is thought that contracting or attempting to contract muscles in synchrony with ES results in better outcomes [19]. Therefore, in this thesis, the main differentiation between cyclical ES and FES is that FES is combined with an activity, whereas cyclical ES is not.

Electrical stimulation may be particularly useful for people who are very weak and who cannot voluntarily contract their own muscles. In this case, it is thought that ES stimulates the large diameter motor units (Type II), causing a tetanic contraction of the muscle [92]. This however is not the order of motor unit recruitment seen when muscles are voluntarily contracted. Type I motor units are usually recruited first as they are slow-twitch (slow to contract and relax) and are fatigue resistant [92]. Type II motor units are then recruited if more force is required or Type I motor units begin to fatigue. This is because Type II motor units are fast-twitch and produce large amounts of force (particularly useful when performing strenuous movements like

lifting heavy objects or climbing flights of stairs), but fatigue quickly and cannot be relied on for prolonged periods [92]. Thus, theoretically, ES used to produce muscle contractions will fatigue muscles faster than a normal physiological muscle contraction. For this reason, many clinicians will instruct patients to use ES for regular short periods of exercise or activity. Over time, ES may increase the activation of motor units and/or the cross sectional area of a muscle by increasing recruitment of muscle fibres [92].

Effects of electrical stimulation on strength after stroke

There is evidence that ES improves strength after stroke. A systematic review (Nascimento et al) investigating the effects of cyclical ES on muscle strength after stroke found a small effect on strength (SMD 0.47, 95% CI 0.26 to 0.68) in favour of ES, when ES was compared to no intervention/placebo [20]. The improvement in strength was maintained beyond the intervention period (SMD 0.33, 95% CI 0.07 to 0.60), although there is a fair amount of uncertainty associated with this estimate. This review was unable to pool studies comparing the effects of cyclical ES with other strengthening interventions due to insufficient post-intervention data. However, interestingly, Nascimento et al was able to differentiate studies that recruited *weak* (able to move the paretic limb through full range of movement against gravity, but had less than normal strength) and *very weak* (unable to move the paretic limb through full range of movement against gravity) participants in the included studies. Meta-analyses on both of these sub-groups revealed that cyclical ES had a small effect on strength of *very weak* participants (SMD 0.40, 95% CI 0.17 to 0.65) and a moderate effect on *weak* participants (SMD 0.66, 95% CI 0.21 to 1.11). When trials were grouped according to time after stroke, cyclical ES had a moderate effect on strength (SMD 0.55, 95% CI 0.28 to 0.81) in people *less than 6 months* after stroke, and a small effect on strength (SMD 0.33, 95% CI -0.02 to 0.69) in people *more than 6 months* after stroke. Similar to the review conducted by Howlett et al, there was

potential for bias in the included studies. All but three of the included studies (13/16) did not conceal group allocation, and 6/16 did not blind assessors to intervention groups.

In summary, we can be fairly confident that there is a small to moderate effect of cyclical ES on strength after stroke, immediately after and beyond the intervention period. There appears to be larger effects on strength in people who are *weak* versus people who are *very weak*, and in people less than 6 months after stroke. However, there is insufficient evidence that cyclical ES is better than other strengthening interventions for improving strength and further trials are needed to investigate the effectiveness of ES versus other strengthening interventions after stroke.

Effects of electrical stimulation on activity after stroke

Two systematic reviews have investigated the effects of ES on activity in people after stroke [19 20]. Both of these reviews reported a small treatment effect when pooling studies that compared ES to no intervention/placebo. However, there was considerable uncertainty associated with both estimates (SMD 0.30, 95% CI 0.05 to 0.56) [20] (SMD 0.40, 95% CI, 0.08 to 0.72) [19] making it difficult to establish the effect size of ES on activity for the whole population of people after stroke. Both reviews also used SMD, making it difficult to interpret the clinical importance of these improvements on activity in real terms. One important difference between these two reviews is how the ES was applied to people. One review (Nascimento et al) included all studies that investigated the effects of cyclical ES on muscle strength [20], and did not state if the included studies required participants to actively contract their weak muscles. The other review (Howlett et al) *only* included studies investigating the effects of ES when combined with active (or attempts of active) practice of an activity (FES). [19] This distinction may be important because the former review may have included studies

where participants were not required to actively contract their weak muscles in synchrony with the ES (i.e. passive ES). Passive ES without attempts to perform an activity may not be the optimal way to improve activity, given our understanding of neuroplasticity and the context-specific adaptions to the central nervous system that occur with active practice. Interestingly, when Howlett et al performed a meta-analysis on studies that compared FES with active practice versus active practice alone, the effect size was greater than the estimate comparing FES versus no intervention/placebo (SMD 0.56, 95% CI 0.21 to 0.92) versus (SMD 0.40, 95% CI 0.08 to 0.72). It is unclear why the effect size was greater in one analysis compared to the other. It would make more sense for the effect to be greater when FES is compared to no intervention/placebo, however this was not the case. One possible explanation is that there may be important differences in the studies included in these different analyses. For example, the analysis of FES versus no intervention/placebo included six trials of upper-limb training and two trials of lower-limb training, and all but one trial included participants in the late stage of stroke recovery. Whereas, the analysis of FES versus active practice alone included six trials of lower-limb training and three trials of upper-limb training, and only three of the nine trials included participants in the late stage of stroke recovery. There may be differences in the way people respond to FES depending on which limb (upper versus lower) or what stage of stroke recovery (early versus late). Therefore, the results of subgroup analyses may help clinicians decide when to use FES, particularly because FES is not always easy to apply or use, not always tolerated by people, and may not deliver clinically important outcomes when compared with active practice without FES. A very important issue with the review conducted by Howlett et al is the quality of the included studies. Over half of the included studies (10/18) did not conceal group allocation, and half (9/18) did not blind assessors to group allocation. These issues may have introduced bias into the included studies, which may have inflated the treatment effects.

In summary, there is uncertainty regarding the effects of cyclical ES or FES on activity due to the content of interventions (i.e. active ES or passive ES) of included studies in the review of cyclical ES, imprecision of estimates (reviews of cyclical ES and FES), and quality of the included studies (review of FES). There appears to be a small to moderate effect of FES when applied to weak muscles while practicing an activity [19]. However, it is not clear whether these estimates are clinically meaningful because results are expressed as SMD.

Robotics

Robotics or electromechanical training has been used in recent years to facilitate large amounts of repetitive training of the paretic upper and lower limbs after stroke. This intervention reduces dependency on therapists, particularly for people who are too weak and disabled to perform independent training. Robot-driven devices, such as exoskeletons or gait orthoses with a harness over a treadmill, are used to mechanically assist people move the paretic lower limb during gait training [95]. Other robotic devices assist people move the paretic upper limb during reaching activities or manipulation tasks, and can provide varying amounts of assistance, resistance to active movement, and greater amplitudes of movement [12].

Effects of robotics on strength after stroke

The effects of robotic-assisted or electromechanical training on strength after stroke has only been investigated in one recent systematic review of the upper limb [12]. This review found a small effect of robotic-assisted or electromechanical training on strength of the paretic upper limb (SMD 0.46, 95% CI 0.16 to 0.77), when compared to other interventions to improve ADLs or upper limb function. However, there was considerable statistical heterogeneity (I^2 = 76%) in the studies included in this analysis suggesting that a meta-analyses was not appropriate. Therefore the results should be interpreted with caution. One interesting aspect of this review is the comparison, namely robotic-assisted or electromechanical training versus *any other*

intervention. As the authors identified, most studies in this review were dose-matched with an active control group. This means that robotic-assisted or electromechanical training was superior to other forms of active upper limb therapy. The reasons for this superiority could not be fully explored in the review due to the lack of reporting of the interventions in the included studies. However, the authors suggested that the robotic devices may have increased the amount of repetitions of active practice over the same amount of time as the other forms of therapy, thus increasing the dose of upper limb therapy delivered to participants.

In summary, there is some evidence to suggest that robotic-assisted or electromechanical training improves upper limb strength more than other therapies after stroke. The exact mechanism by which this happens is unclear, but may be due to a larger amount of repetitions of active practice facilitated by the robotic device.

Effects of robotics on activity after stroke

There are two Cochrane systematic reviews investigating the effects of robotic-assisted or electromechanical training on activity after stroke [11 12]. One review specifically investigated the effects of electromechanical-assisted training on walking [11]. This review found that when provided in addition to physiotherapy the odds of people becoming independent walkers increased (OR 1.94, 95% CI 1.39 to 2.71). However, there was no significant increase in walking velocity or walking capacity with this intervention. The other review investigated the effects of robotic-assisted or electromechanical training on activities of daily living (ADL), upper limb function and strength [12]. This review found that when compared to other interventions to improve ADLs or upper limb function, there is a small effect of robotic-assisted or electromechanical training on ADLs (SMD 0.31, 95% CI 0.09 to 0.52) and upper limb function (SMD 0.32, 95% CI 0.18 to 0.46). While these results both represent a small treatment

effect, they need to be interpreted with caution since 31/45 trials in the review did not report methods of concealed allocation and only 3/45 trials had reported all outcomes according to the registered protocol. These methodological issues in the included studies may have introduced bias and therefore we should have less confidence in the results.

In summary, there is some indication that robotic or electromechanical training of walking, in addition to usual physiotherapy, increases the odds of people becoming independent walkers. There is also evidence that ADLs and upper limb function are improved with robotic-assisted or electromechanical training. However, these results need to be interpreted with caution due to small sample sizes and methodological issues of the included studies. Further large high-quality trials are needed to clarify the effects of robotic or electromechanical training on activity after stroke.

Constraint-Induced Movement Therapy

Constraint-induced induced movement therapy (CIMT) of the upper limb is described as therapy consisting of two fundamental principles:

- Restraint of the non-paretic upper limb (i.e. using an arm sling and a resting hand splint). A behavioural contract is drawn up between the participant and therapist with the goal of restraining the non-paretic upper limb for approximately 90% of waking hours.
- Mass practice of the paretic upper limb over several hours per day, using a method called ‘shaping’. The shaping procedure has been described as follows: (a) providing explicit verbal feedback and verbal reward for small improvements in task performance; (b) selecting tasks that are tailored to address the motor deficits of the individual patient; (c) helping the patient to carry out parts of a movement sequence, if they are incapable of

completing the movement on their own at first; and (d) systematically increasing the difficulty level of the task performed [96].

Constraint-induced movement therapy aims to overcome learned non-use of the paretic upper limb by forcing the person to use their paretic upper limb to perform motor tasks. Early studies of CIMT proposed between six and eight hours of training per day [97 98]. However, more recent studies have investigated modified approaches of delivering CIMT, i.e. reducing the amount of motor training while the restraint is in-situ, or restraining the non-paretic upper limb without additional motor training [99-102]. Clinical trials and systematic reviews have divided CIMT into three different types, based on the dosage or content of training. Studies that performed CIMT for more than three hours are considered to have provided usual CIMT. Studies that performed CIMT for less than three hours are considered to have provided modified CIMT (mCIMT), and studies that restrained the non-paretic upper limb without additional training of the paretic upper limb are considered to have provided Forced Use therapy [13].

Effects of constraint-induced movement therapy on strength after stroke

Prior to this research program, the effects of CIMT on muscle strength had not been investigated in a systematic review. One systematic review investigated the effects of CIMT on different aspects of motor impairment, but did not focus specifically on voluntary muscle strength, and combined data from different motor impairments in a SMD [13]. Unsurprisingly, there was considerable statistical heterogeneity in the analysis on motor impairment ($I^2 = 77\%$) in this review. This review also combined studies that provided an active control group with those that provided no intervention/placebo, making it difficult to determine the effects of CIMT alone. One randomised controlled trial compared six hours of CIMT per day with a 30 minute per day independent exercise program [103]. After two weeks, the mean between-group

difference (95% CI) for hand-grip strength was 0.8 kg (0.26 to 1.34) in favour of CIMT. This was a small study of 18 participants, and it is unclear if investigators or assessors were blinded to group allocation. Therefore, these results need to be interpreted with caution.

In summary, there appears to be evidence that CIMT improves upper limb strength more than providing an independent exercise program. However, the results of this small trial with unclear methods needs to be interpreted with caution. A systematic review including more trials will clarify the effects of CIMT on upper limb strength.

Effects of constraint-induced movement therapy on activity after stroke

A Cochrane systematic review comparing CIMT to usual care or no intervention found that CIMT improves upper limb motor function (SMD 0.34, 95% CI 0.12 to 0.55), motor impairment (SMD 0.82, 95% CI 0.31 to 1.34) and dexterity (SMD 0.42, 95% CI 0.04 to 0.79) [13]. Despite these improvements in impairment and motor function there was no reduction in disability (SMD 0.24, 95% CI -0.05 to 0.52). The results for disability were derived from 11 small studies of 344 participants. It is difficult to understand how CIMT can improve motor function of the upper limb, but have no impact on disability. There could be several reasons to explain this. Firstly, the insignificant estimate on disability may reflect how disability was measured in the review. The authors limited this outcome to the Functional Independence Measure and the Barthel Index. There may be other outcome measures that measure disability that were not included in the meta-analysis. Alternatively, there may not be an effect on disability with CIMT. However, the imprecise estimate on disability suggests that the sample size was too small (i.e. too few participants or too few studies) to attain a precise estimate of the treatment effect, indicating that the effect of CIMT on disability is inconclusive, rather than ineffective. Estimates from sub-group analyses were also imprecise in this review. For

example, when comparing studies that provided more than 30 hours of CIMT to those that provided less, there were only 3 studies with 91 participants that provided more than 30 hours of CIMT. However, there were 8 studies with 253 participants that provided less than 30 hours of CIMT. Whilst both estimates for these sub-groups were imprecise (>30 hours, SMD 0.25, 95% CI -0.18 to 0.67) versus (<30 hours, SMD 0.18, 95% CI -0.07 to 0.44), the estimate of the subgroup with more participants was more precise. Many studies in the analysis on disability were also dose-matched with an active control group performing functional training of the upper limb. This may have introduced clinical heterogeneity into the analysis, since people in the control groups of some studies could have performed large amounts of active practice, whilst people in other studies performed no active practice. The quality of included studies in this review was highly variable with many studies subject to high or uncertain amounts of bias.

In summary, there is evidence that CIMT improves upper limb activity more than usual care after stroke. However, there is still uncertainty regarding the effects of CIMT on disability. Further large high-quality trials comparing CIMT with usual care are needed to clarify the effects of CIMT on disability after stroke.

Task-specific training

Task-specific training is a term that has evolved from movement science and motor skill learning literature [104]. This type of training or therapy is where participants practice motor tasks whilst receiving feedback (i.e. visual or verbal feedback) [105]. The focus of task-specific training is on goal-directed practice and repetition of a task to improve performance of that task, rather than purely focusing on improving impairments, such as strength [105]. Task-specific training incorporates active cognitive involvement of the participant in tasks that are

relevant and meaningful (i.e. standing up or walking practice), and feedback of the performance of tasks to enhance motor skill acquisition [106 107].

Effects of task-specific training on strength after stroke

There is no systematic review specifically investigating the effects of task-specific training on strength after stroke. Systematic reviews on the topic have included studies of progressive resistance training [108-112] or an artificial drive of muscle contraction [20 113] (i.e. electrical stimulation without attempts to move a limb) as an intervention. Combining these interventions in a systematic review is problematic, since there may be differences in the mechanisms underlying the observed effects on strength. There may also be differences in the samples of the included studies of each review. For example, people participating in a clinical trial of progressive resistance training may be far stronger and less disabled than people who participate in a trial of task-specific training. This is due to the emphasis on low repetition and added resistance with progressive resistance training (see next section). Some people after stroke are too weak to contract their muscles against added resistance, and therefore cannot participate in a trial investigating the effects of progressive resistance training. One randomised controlled trial investigating the effects of a 52-week task-specific lower limb exercise class reported a non-significant mean between-group difference (95% CI) in knee extensor strength of 0.95 kg (-1.2 to 3.1) in favour of task-specific training (18.3 kg = mean baseline strength) [114]. This high-quality trial with minimal bias was conducted with 133 people, approximately 6 years after stroke and compared task-specific lower limb training to no intervention/placebo. Another randomised control trial investigating the effects of a four-week task-specific upper limb exercise program reported a statistically significant mean between-group difference (95% CI) in hand-grip strength of 2.1 kg (0.49 to 3.71) in favour of task-specific training (8.8 kg = mean baseline strength) [115]. This high-quality trial with minimal bias was conducted with

103 people, approximately less than one month after stroke and compared task-specific upper limb training to no intervention/placebo. Based on these two trials there are clear differences in the effects of task-specific training on strength. These differences in effects are probably due to the time after stroke (early versus late) and the limbs that were trained (lower limb versus upper limb). However, we would be more certain of the effects of task-specific training on strength if these results were repeated in other clinical trials or confirmed in a systematic review of multiple trials.

In summary, based on these trials, there appears to be evidence that task-specific training of the upper-limb improves hand-grip strength in the early stages of stroke recovery. There is also evidence that task-specific training does not improve lower limb strength in the late stages of stroke recovery. However, these results need to be interpreted with caution because they are only from two trials. A systematic review including more trials will clarify the effects of task-specific training on upper and lower limb strength, in the early and late stages of stroke recovery.

Effects of task-specific training on activity after stroke

Task-specific training of the paretic upper and lower limbs is recommended in evidenced-based guidelines as the primary therapy to improve activity and reduce disability after stroke [10]. These recommendations are based on multiple systematic reviews investigating the effects of repetitive task-specific training on various tasks after stroke. The reviews found improvements in upper limb activity (SMD 0.25, 95% CI 0.01 to 0.49) [9], walking distance (MD 35m, 95% CI 18 to 51) [9], walking speed (MD 0.06 m/s, 95% CI 0.03 to 0.09) [14], functional ambulation (SMD 0.35, 95% CI 0.04 to 0.66) [9] and sit-to-stand ability (OR 4.86, 95% CI 1.43 to 16.50) [116] with task-specific training. All but one [14] of these estimates refer to a comparison of

the task being trained versus no intervention/placebo. Each systematic review individually assessed the quality of the evidence based on the GRADE criteria, taking into consideration risk of bias, imprecision, inconsistency, indirectness, and publication bias of the included studies. Overall, the estimates for upper limb activity and sit-to-stand ability represent low and very low-quality evidence, respectively. Whereas, the estimates for walking distance, walking speed and functional ambulation represent moderate quality evidence. The main reasons for downgrading evidence to low and moderate quality were due to poor reporting of methods. For example, one review found that only eight of the 33 trials included in their meta-analysis, reported adequate methods of allocation concealment [9]. Another review, only found one trial investigating the effects of sit-to-stand training on sit-to-stand ability. The reviewers downgraded the evidence to very low-quality due to the high risk of bias in random sequence generation and allocation concealment in the trial [116]. These methodological issues need to be taken into consideration when deciding if task-specific training (or any other intervention) is effective for improving activity after stroke. As discussed in other sections, it is also important to consider the precision and clinical importance of these estimates. For example, it is easier to decide if the estimates for walking distance and walking speed are clinically worthwhile, since the estimates are reported as a MD. However, the imprecision of the estimates and the use of SMD (i.e. upper limb activity and functional ambulation) make it difficult to determine if task-specific training of those tasks is clinically worthwhile.

In summary, there is moderate quality evidence that task-specific training of walking improves walking. There is also low-quality evidence for task-specific upper limb training and very low-quality evidence for sit-to-stand training. Further clinical trials are needed to clarify the clinical importance of treatment effects for task-specific upper limb training and sit-to-stand training.

Progressive Resistance Training

Progressive resistance training (as defined by the American College of Sports Medicine) is characterised by muscles working at high loads with low repetitions, that is, a load of 8 to 12 repetitions of 60-70% of 1 repetition maximum, for at least two sets, with a progressive increase of the load [117]. Progressive resistance training can be performed using large machines, free weights, or rubber resistance bands, and commonly involves single- or multi-joint muscle groups [117 118].

Progressive resistance training is commonly used to improve strength in people without disability [117] and frail older people [119]. However, PRT is not commonly used in stroke rehabilitation despite the large improvements in strength that have been observed in frail older people and people without disability [119 120]. Therefore, this section will discuss the evidence for PRT in these three populations suggesting reasons why PRT may not be commonly utilised as a strengthening intervention after stroke.

People without disability

The American College of Sports Medicine (ACSM) is considered by many as the leading authority on guidelines for prescription of PRT. The ACSM guidelines recommend that adults perform resistance training for each of the major muscle groups 2 to 3 times per week [117]. The evidence underpinning these guidelines comes from randomised controlled trials and systematic reviews about PRT in adults without disability. Interestingly, the systematic reviews referred to in the ACSM guidelines have largely compared doses of PRT regimes rather than investigating the effects of PRT versus no training [121-123]. A more recent systematic review not included in the ACSM guidelines investigated the effects of PRT versus no training in older (≥ 60 years) adults without disability [120]. This review of 25 randomised controlled trials and

a total of 819 participants reported a between-subject standardised mean difference (SMD_{bs}) of 1.57, 95 % CI 1.20 to 1.94 in favour of PRT when upper and lower limb studies were combined. Subgroup analyses of upper and lower limb were SMD_{bs} 1.61, 95 % CI 0.95 to 2.27 and SMD_{bs} 1.76, 95 % CI 1.20 to 2.31, respectively. These point estimates represent large effects of PRT on upper and lower limb strength in older adults without disability when compared to no training. However, these estimates need to be interpreted with caution due to the high levels of statistical heterogeneity in the analyses (I^2 = 80 % - upper and lower limb combined, I^2 = 86 % - upper limb, I^2 = 87 % - lower limb), suggesting that meta-analyses should not have been performed. Furthermore, most studies in this systematic review were of low methodological quality with an average PEDro scale rating of 4.6/10 points. Studies with low methodological quality may have introduced bias into the meta-analyses, therefore, this issue should also be taken into consideration when interpreting the results. Taken together, the results from this systematic review and the systematic reviews referred to in the ACSM guidelines suggest that PRT is an effective strengthening intervention for people without disability.

Older people

One systematic review investigating the effects of PRT in older people living in the community (including frail and disabled people) found a moderate to large improvement in strength (SMD 0.84, 95% CI 0.67 to 1.00) when PRT was compared to no intervention/placebo [119]. Interestingly, large improvements in strength with PRT translated into small reductions in disability (SMD 0.14, 95% CI 0.05 to 0.22) and small improvements in activity (walking speed = MD 0.08 m/s, 95% CI 0.04 to 0.12; mobility (TUG) = MD -0.69 secs, 95% CI -1.11 to -0.27; chair rise time = SMD -0.94, 95% CI -1.49 to -0.38). This finding supports the hypothesis of a curvilinear relationship between strength and activity, suggested by Buchner et al 1996, where small improvements in muscular strength in people who are weak translate into large

improvements in activity [68]. However, decisions regarding the clinical importance of effects on activity are subjective, dependent on the activity, and need to take into account clinical implications, such as harm, costs and inconvenience to participants and clinicians.

Effects of progressive resistance training on strength after stroke

The effect of PRT on strength after stroke has been investigated in several systematic reviews [109-112 124]. However, all but one of these reviews [124] included studies that did not follow a strict definition of PRT, as defined by the ACSM [117]. The systematic review by Dorsch et al 2018, compared PRT to no intervention/placebo. This review found large improvements in strength of the paretic upper and lower limbs with PRT (SMD 0.98, 95% CI 0.67 to 1.29). These results were from a meta-analysis of six trials (with an average methodical quality score of 5.8/10 (PEDro scale)) involving 163 participants. The precision of the point estimate was fairly wide but still ranged from a moderate to large treatment effect. One limitation of this review was that it excluded three trials because they did not report change data. Inclusion of these trials might have increased precision around the point estimate, thus providing a more precise estimate of PRT on strength. More importantly, excluding these three trials from the systematic review may have introduced bias into the analysis, because there may be important differences in these studies that should be included in the estimates. Another limitation of this review is generalisability. All but one of the studies in the meta-analysis on strength included participants more than one year after stroke. Therefore, these results can only be generalised to people in the later stages of stroke recovery. None-the-less, given these results from a high-quality systematic review, we can be confident that PRT improves strength after stroke.

In summary, there is high-quality evidence that PRT improves strength after stroke. However, these results are only applicable to people in the late stages of recovery and cannot be generalised to people in the early stages.

Effects of progressive resistance training on activity after stroke

A recent systematic review investigating the effects of PRT on strength and activity after stroke found that PRT improved strength, but these improvements in strength did not translate into improvements in activity (SMD 0.42, 95% CI -0.08 to 0.91) [124]. It is difficult to understand how improvements in strength do not translate into improvements in activity, since people after stroke can be very disabled as a result of muscle weakness. However, there are a few issues to consider when interpreting these findings. Firstly, there is great imprecision around the point estimate on activity, therefore, we cannot rule out a treatment effect as these results appear to be inconclusive. Secondly, the primary outcome for this review was voluntary strength; therefore, studies that only measured activity were excluded from this review. Thirdly, the outcome measures used to measure activity in the included studies may not have accurately reflected the muscles that were trained with PRT. For example, improving knee extension strength in people who already have sufficient knee extension strength to weight-bear may not improve walking speed (a common measure of lower limb activity). Taken together, these issues suggest that there may be improvements in activity with PRT in people after stroke. Other important issues to consider when interpreting these results are 1) how the included studies administered PRT and 2) how activity was measured. For example, on closer examination of the three studies demonstrating a statistically significant treatment effect on activity, investigators from one study administered PRT as part of a package of exercises that included repetitive task training [125]. Repetitive task training is conceptually very different to PRT and it would be impossible to separate the effects of one intervention from the other when

measuring activity. In other words, the effects of PRT on activity in that study were from a package of repetitive task training and PRT combined, and not the effects of PRT alone. Another study [126] in this meta-analysis measured activity using an impairment scale which also measures voluntary muscle strength. This may have inflated the treatment effect of PRT on activity in this study, since PRT improves strength. The third study [127] demonstrating a treatment effect in the meta-analysis on activity measured activity with many other outcome measures and it was not clear what the primary outcome measure was or when it was determined. This issue may have produced a Type II error, meaning that the observed effect on activity in that study may have purely been due to chance. These issues all affect the interpretation of the results from this meta-analysis causing more uncertainty regarding the effect of PRT on activity.

Finally, one other issue to consider is that it is possible that there are no improvements in activity with PRT after stroke. That is, it could be that people who are strong enough to participate in PRT may already have higher levels of activity. Therefore, merely improving muscle strength may not be enough to improve activity in those who are stronger after stroke. However, this explanation is difficult to reconcile with evidence from another large systematic review that found a treatment effect of PRT on activity in frail older people [119]. This is because it is possible that frail older people have higher levels of activity than people after stroke; therefore, improving muscle strength in a population that is less active is more likely to affect activity than improving strength in a population that is more active.

In summary, there is uncertainty regarding the therapeutic effects of PRT on activity after stroke. Evidence from systematic reviews is conflicting and trials have not conclusively

answered this question. Further large trials with minimal bias are needed to clarify the effects of PRT on activity after stroke.

This section has reviewed the evidence for PRT after stroke. It is interesting that there are comparatively few studies (n = 9) investigating the effects of PRT, especially when large improvements in strength can be made in a population where muscular weakness is common. However, there may be several reasons for this. One reason could be due to the historical belief that effortful muscular contractions increased spasticity, which in turn increased activity limitations and disability [128]. This belief has since been disproven [108 109], however, it is possible that this belief still exists to some extent in clinical practice, despite the research evidence. It could also be that clinicians who once believed PRT increased spasticity do not know how to apply the principles of PRT. These clinicians then go on to train students and less experienced clinicians using incorrect principles and techniques. Another reason could be that PRT is difficult to perform correctly in people with very weak muscles. That is, due to neurological activation failure people may be too weak to move a limb against external resistance, or may not be able to consistently move a limb through full range of movement against gravity. These criteria are required to perform PRT as defined by the ACSM [118 129]. Therefore, studies investigating the effects of PRT would require participants to be strong enough to participate in the intervention. However, muscular weakness is often not the only impairment people experience after stroke and clinicians (or researchers) may choose to prioritise repetitive task training which incorporates strength, coordination, sensory input and cognitive demands, whilst training a task that is challenging for the participant. Unlike PRT, there is also an established evidence base from high-quality systematic reviews that repetitive task training improves activity after stroke. Therefore, clinicians may choose to prioritise repetitive task training in the clinic (or in research) over PRT as the most effective and efficient

intervention to improve activity. This prioritisation of repetitive task training may be appropriate for individuals who are too weak to participate in PRT, however, repetitive task training may not be the optimal intervention for people who are strong enough to participate in PRT. Since there is uncertainty regarding the effectiveness of PRT on activity, further large randomised controlled trials with minimal bias are needed to clarify the effects of PRT on activity in this group of people after stroke.

Summary

This section has critically reviewed five strengthening interventions in the management of weakness after stroke. Four of these interventions (ES, Robotics, CIMT, and Task-specific training) are commonly used in stroke rehabilitation programs because they can facilitate repetitive training in very weak muscles. These four interventions also have evidence from meta-analyses that they improve activity after stroke. However, there is less evidence that these interventions improve strength and systematic reviews have not investigated this issue for any of these interventions. Progressive resistance training on the other hand is not commonly used in stroke rehabilitation, probably because PRT is difficult to perform correctly in people with very weak muscles, and is conceptually very different to the other four interventions. That is, PRT requires low repetitions with muscles working against high loads with progressive overloading of the muscles being trained. Contrary to the other four interventions, there is strong evidence that PRT improves strength after stroke, however there is no clear evidence that PRT improves activity. All five interventions have systematic reviews of their effects on activity with robust methodologies, however, many of the included studies are subject to high or uncertain amounts of bias. Included studies are also small and estimates on activity are often imprecise. Few of the included studies reported how weak participants were or how many

repetitions of training participants performed. This lack of reporting prevented sub-group analyses in systematic reviews.

This literature review has highlighted the gap in current knowledge of the effects of repetitive practice on strength and the possible mechanisms underlying the observed improvement in activity after stroke. A systematic review of interventions involving repetitive practice is needed to determine if improvements in strength are accompanied by improvements in activity. This knowledge will assist therapists and healthcare providers when prioritising which interventions are more likely to improve both strength and activity in stroke rehabilitation programs.

Dosage of motor training

The dosage (amount) of motor training required to reduce activity limitation after stroke is difficult to determine. Systematic reviews have quantified dosage of training using time spent in therapy or practice [25-27 130 131]. However, time spent in therapy is a poor indicator of dosage. For example, an observational study in people after stroke found that the range of repetitions of exercise in 30-minute sessions of therapy was 4 to 369 repetitions [132]. Therefore, repetitions of active exercise (or movement) are a far better indicator of dosage of motor training than time spent in therapy.

To quantify the amount of repetitions required to reduce activity limitation, researchers initially performed studies in rats and monkeys [133-135]. These studies demonstrated structural neurological changes in the primary motor cortex of the brain and improvements in upper limb function with 400 to 600 repetitions of upper limb motor training per day. In humans, observational studies investigating the effects of repetitive upper limb motor training reported

improvements in upper limb function with 300 to 800 repetitions of motor training per session [136 137]. However, results from clinical trials of dosage have been conflicting. One trial in the early phase [138] and one trial in the late phase (>6 months) [139] after stroke did not demonstrate significant improvements in upper limb function with different doses of task-specific motor training. The intervention groups in the trial in the early phase ranged from usual therapy (control) to three hours of CIMT per day for two weeks, whereas the intervention groups in the trial in the late phase ranged from 100 repetitions to 300 repetitions of motor training per session over eight weeks. Similarly, another recent trial which randomised 45 participants into four intervention groups ranging from 0 to 60 hours of motor training in the late phase of stroke recovery, did not demonstrate improvements in upper limb function. Interestingly, this trial demonstrated improvements in upper limb *use*, rather than function, with 60 hours of motor training over three weeks [140]. There could be several reasons for the lack of a treatment effect in these trials, however, the most obvious reason could be that 3 hours of CIMT or 300 repetitions of upper limb motor training per session may not be sufficient to improve upper limb function.

In the lower limb, there are few studies that have reported amount of repetitions of motor training. Two randomised controlled trials investigating the effects of sitting balance training in the early [141] and late [142] phases of stroke recovery reported improved sitting balance with approximately 300 repetitions of sitting balance training per day for two weeks. A cohort study designed to predict walking outcomes after stroke found that people who performed more than 700 repetitions of lower limb exercises in the first week of rehabilitation were much more likely to walk 20 days after commencing rehabilitation than people who had not [143]. Furthermore, of those who performed more than 700 repetitions of lower limb exercise in the first week, 80% were able to walk independently at 20 days. However, in contrast, only 20%

of those who did not perform more than 700 repetitions of lower limb exercise were able to walk independently at 20 days. This study was designed to predict walking outcomes and should not be used to imply causation. Nonetheless, these results in combination with the other evidence point to a dose-response relationship between amount of repetitions of motor training and improvement in activity in the lower limb.

Summary

Together these studies do not provide specific amounts of repetitions required to improve individual upper and lower limb tasks such as reaching and manipulation, sitting, or walking. To do this, many larger randomised controlled trials testing different amounts of training with different sub-groups of people (i.e. weak versus very weak) after stroke are needed. However, when making decisions regarding amount of motor training clinicians need to take into consideration the costs involved in providing an intervention, harms, and inconvenience to a person (therapist providing or person receiving the intervention). There is a difference between the amount of motor training needed to reduce activity limitation and what is clinically feasible or safe for a person after stroke. For example, in the case of upper limb training, 3 hours of CIMT per day or 300 repetitions of upper limb motor training per session in addition to other therapies (such as speech or lower limb motor training) may not be feasible. Furthermore, the potential benefits of larger amounts of upper limb motor training may be too small to be meaningful to people who have other impairments and activity limitations that they want to improve. None-the-less, these studies of dosage indicate that large amounts (hundreds per day) of repetitions are required to improve functional tasks, and possibly larger amounts of repetitions of motor training are required to improve the upper limb tasks than lower limb tasks. The conflicting results between observational studies and randomised controlled trials of the upper limb may be due to study design. That is, cohort studies are not the appropriate research

designs for investigating causal links unless they are large and have appropriately controlled for confounding factors.

Chapter 3 Interventions involving repetitive practice improve strength after stroke: a systematic review

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Published manuscript

This project is presented as a published manuscript:

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1. **de Sousa DG**, Harvey LA, Dorsch S, Glinsky JV. Do interventions involving repetitive practice improve strength after stroke? A systematic review. Proceedings of the World Confederation for Physical Therapy, Geneva, Switzerland, 2019.

2. **de Sousa DG**, Harvey LA, Dorsch S, Glinsky JV. Do interventions involving repetitive practice improve strength after stroke? A systematic review. Smart Strokes, Hunter Valley, Australia, 2019.

Publication statement

Statement from co-authors confirming the authorship contribution of the PhD candidate. As co-authors of the manuscript:

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We confirm that Davide de Sousa has made the following contributions:

- Conception and design of the research including literature search
- Collection of data
- Analysis and interpretation of the findings
- Writing the manuscript, critical appraisal of content and response to reviewers

Name	Signature	Date
Lisa Anne Harvey		30-Aug-2019
Simone Dorsch		30-Aug-2019
Joanne Valentina Glinsky		30-Aug-2019

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Research

Interventions involving repetitive practice improve strength after stroke: a systematic review

Davide G de Sousa [a,b,c], Lisa A Harvey [b,c], Simone Dorsch [d], Joanne V Glinsky [b,c]

[a] Graythwaite Rehabilitation Centre, Ryde Hospital; [b] John Walsh Centre for Rehabilitation Research, Kolling Institute; [c] Sydney Medical School Northern, University of Sydney; [d] Faculty of Health Sciences, Australian Catholic University, Sydney, Australia

KEY WORDS

Stroke
Strength
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Meta-analysis

ABSTRACT

Questions: Do interventions involving repetitive practice improve strength after stroke? Are any improvements in strength accompanied by improvements in activity? **Design**: Systematic review of randomised trials with meta-analysis. **Participants**: Adults who have had a stroke. **Intervention**: Any intervention involving repetitive practice compared with no intervention or a sham intervention. **Outcome measures**: The primary outcome was voluntary strength in muscles trained as part of the intervention. The secondary outcomes were measures of lower limb and upper limb activity. **Results**: Fifty-two studies were included. The overall SMD of repetitive practice on strength was examined by pooling post-intervention scores from 46 studies involving 1928 participants. The SMD of repetitive practice on strength when the upper and lower limb studies were combined was 0.25 (95% CI 0.16 to 0.34, I^2 = 44%) in favour of repetitive practice. Twenty-four studies with a total of 912 participants investigated the effects of repetitive practice on upper limb activity after stroke. The SMD was 0.15 (95% CI 0.02 to 0.29, I^2 = 50%) in favour of repetitive practice on upper limb activity. Twenty studies with a total of 952 participants investigated the effects of repetitive practice on lower limb activity after stroke. The SMD was 0.25 (95% CI 0.12 to 0.38, I^2 = 36%) in favour of repetitive practice on lower limb activity. **Conclusion**: Interventions involving repetitive practice improve strength after stroke, and these improvements are accompanied by improvements in activity. **Review registration**: PROSPERO CRD42017068658. **[de Sousa DG, Harvey LA, Dorsch S, Glinsky JV (2018) Interventions involving repetitive practice improve strength after stroke: a systematic review. *Journal of Physiotherapy* 64: 210–221]**

Introduction

The loss of strength after stroke is a common and important impairment. The average strength of the affected upper and lower limb in people who have had a significant stroke ranges from 30 to 50% of age-matched controls.[1–4] This loss of strength can result in profound activity limitations[5–7] and participation restrictions.[8] Therefore, it is important to know which interventions are effective for improving strength after stroke. Progressive resistance training is commonly used to improve strength in people without disability[9] and can be used to improve strength in people after stroke.[10] Progressive resistance training is characterised by muscles working at high loads with low repetitions, that is, a load of 8 to 12 repetitions maximum (RM) for at least two sets with a progressive increase in the load.[9] However, progressive resistance training is not commonly used after stroke, and often when strengthening programs claim to be using progressive resistance training they are not adhering to the guidelines.[11] This may be because progressive resistance training is time-consuming to set up and difficult to implement in people with very weak muscles. In contrast, repetitive practice of tasks can be set up with minimal equipment and modified so that even people with very weak muscles can do some form of training.

Repetitive practice of tasks, such as walking, reaching and manipulation of objects, is a major component of rehabilitation after stroke. Some interventions used to promote repetitive practice include constraint-induced movement therapy, treadmill walking with body-weight support, or robotic devices. These interventions are typically performed with an emphasis on high repetitions and no added resistance to movement; hence, the principles of repetitive practice are very different to the principles of progressive resistance training. Repetitive practice is known to be effective for reducing activity limitations, with many systematic reviews confirming this.[12–15] However, less is known about the effects of repetitive practice on strength after stroke, and no systematic reviews have specifically investigated this issue. Eight systematic reviews with meta-analyses have investigated the effects of strengthening interventions on strength after stroke. These reviews included studies that used progressive resistance training[10,16–20] or an artificial drive of muscle contraction[21,22] (ie, electrical stimulation without attempts to move a limb) as an intervention and did not focus specifically on repetitive practice.

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Since repetitive practice is widely used and recommended in rehabilitation after stroke,[23] it is important to understand if interventions involving repetitive practice are effective for improving strength.

Therefore, the research questions for this systematic review were:

1. Do interventions involving repetitive practice improve strength after stroke?
2. Are any improvements in strength accompanied by improvements in activity?

Box 1. Inclusion criteria.

Design
- Randomised

Participants
- Adults (> 18 years old)
- Diagnosis of stroke

Intervention
- Repetitive practice

Comparisons
- Repetitive practice versus no intervention
- Repetitive practice versus a sham intervention

Outcome measures
- Muscle strength measured as maximum force/torque, or composite scales of multiple muscle groups, or manual muscle testing, measured immediately after the intervention in the muscles that were trained

Method

Identification and selection of studies

Participants

Studies involving adult participants of either gender at any time after stroke were included. Studies that also involved participants with other types of acquired brain injury (eg, trauma) were excluded unless > 80% of participants had a diagnosis of stroke.

Intervention

Studies that examined the effectiveness of interventions that involved repetitive practice on land or in water (ie, hydrotherapy or aquatic physiotherapy) were included. Repetitive practice was defined as repetitive voluntary contraction of muscles of the affected upper or lower limb and included repetitive practice of a whole task (eg, sitting, standing up, walking) or components of a task (eg, elbow extension/flexion as a component of reaching and manipulation). Where constraint-induced movement therapy was used, studies that merely constrained the unaffected upper limb without active practice using the affected upper limb were excluded. Studies were excluded if: the intervention only included an artificial drive of muscle contraction (eg, passive robotics or electrical stimulation without attempts to move a limb), the intervention did not require voluntary muscle contraction (eg, mental practice, massage, passive movement), or the intervention involved progressive resistance strength training (ie, 1 to 3 sets, 8 to 12 repetitions of 60 to 70% 1RM with progression of resistance).

Comparison

The comparisons of interest were no intervention or a sham intervention. Studies with co-interventions were included provided the co-intervention was delivered to both groups (eg, repetitive practice plus usual therapy versus usual therapy).

Outcome measures

The primary outcome for this systematic review was strength. Studies were included if one of their outcomes was strength of the affected upper or lower limb in muscles that were trained. Strength could be measured in a number of ways, including: maximum force, maximum torque, manual muscle testing using the Medical Research Council (MRC) scale, or composite scales of multiple muscle groups such as the Motricity Index. Where multiple measures of strength were reported, the measure that best reflected the training was used. For example, if upper limb training primarily involved manipulation tasks, then hand grip strength was chosen rather than elbow extension strength. If studies reported outcomes at multiple time-points, then data collected at the time-point closest to the end of the intervention were extracted.

The secondary outcomes for this systematic review were activity of the affected upper and lower limb, measured using any continuous or ordinal measure of activity. These secondary outcomes were only collected from studies that met the inclusion criteria for the review. That is, studies that measured activity were only included if they also measured strength, because the analysis of activity was a secondary analysis used to determine whether improvements in strength were accompanied by improvements in activity. Where multiple measures of activity were reported, the measure that best reflected the training was used. For example, if the repetitive practice targeted the lower limb, a lower limb measure such as the 10-m walk test was used rather than a measure of upper limb activity. Priority for the upper and lower limb measures of activity were given to the Action Research Arm Test and the 10-m walk test, respectively, because these outcome measures have been recommended for use in clinical studies by the international research community.[24]

Searches were conducted of MEDLINE (Ovid) (1946 to 24 January 2017), EMBASE (Ovid) (1947 to 24 January 2017), AMED (1985 to 24 January 2017), CINAHL (Ebsco) (1982 to 24 January 2017), SCOPUS (inception to 24 January 2017), SPORTDiscus (Ebsco) (inception to 24 January 2017), Web of Science (inception to 24 January 2017), Cochrane Central Register of Controlled Trials (CENTRAL) (1986 to 24 January 2017) and PEDro (inception to 13 February 2017) for relevant studies written in English with no date restrictions. Search terms included words related to stroke, randomised trials, repetitive practice and muscle strength (see Appendix 1 on the eAddenda). Hand searching of the reference lists of the included studies and relevant systematic reviews was undertaken. Authors of conference abstracts were contacted for full reports of unpublished studies. One reviewer independently screened all titles and abstracts to identify relevant studies. All titles and abstracts were also equally divided and independently screened by three other reviewers, ensuring that all titles and abstracts were screened by two people. Full-text copies of relevant studies were retrieved and reviewed independently by each reviewer using predetermined eligibility criteria (Box 1). If two reviewers disagreed about the eligibility of a study, a third reviewer arbitrated until a consensus was reached.

Assessment of risk of bias

One reviewer independently assessed risk of bias of the included studies using the Cochrane Risk of Bias Tool. Each study was rated as high risk, unclear risk or low risk on the following domains: sequence generation; concealed allocation; blinding of participants and therapists; blinding of outcome assessors; incomplete outcome data; selective outcome reporting; and other bias. Studies were checked online against published PEDro scores to assist with decisions regarding bias, and disagreements were resolved by a second reviewer. Studies that reported incomplete data in more than 15% of participants were deemed to have high risk of bias from incomplete outcome data. Studies that did not report a clinical trial registration number or registered the protocol retrospectively were deemed to have unclear risk of bias in the category of 'other bias'.

Data extraction and analysis

Two reviewers independently extracted outcome data and details of the experimental and control interventions. The number of participants, age and time since stroke were recorded to describe the participants. Post-intervention data were retrieved in preference to change data because these were the most commonly provided data and the data needed to be in the same format for meta-analyses expressed as standardised mean differences (SMD). Authors were contacted if there were missing outcome data or post-intervention data were not provided. Differences between the two reviewers were resolved by discussion, and when necessary, arbitrated by a third reviewer.

Separate meta-analyses were performed on studies involving the same intervention for strength, upper limb activity and lower limb activity. Meta-analyses were only considered if there were sufficient data to pool and there was not excessive between-trial heterogeneity (ie, I^2 values were not $\geq 75\%$). A fixed-effect model was used if there was no apparent clinical heterogeneity and the I^2 value was $\leq 50\%$. A random-effects model was used if there was no apparent clinical heterogeneity and the I^2 value was $> 50\%$. Pooled estimates were reported as SMD (95% CI) for all analyses because outcomes were measured in different ways. If post-intervention data were not available, separate meta-analyses were conducted of studies that only provided change data. This was done to avoid pooling of post-intervention data with change data, given that the results of all analyses were reported as SMD.

Sensitivity analyses

Sensitivity analyses were conducted to examine the robustness of the primary meta-analysis for strength. The sensitivity analyses explored the effects of various methodological aspects of the included studies, including: methods for generating the randomisation sequence (only trials with adequate methods); effects of allocation concealment (only trials with concealed allocation); blinding of assessors (only trials with blinded assessors); selective outcome reporting (only trials without selective outcome reporting); incomplete outcome data (only trials with $\leq 15\%$ missing data); and other bias (only trials without other bias).

Subgroup analyses

Subgroup analyses on the strength data were performed to explore four factors. The first subgroup comparison was based on the limbs that were trained (upper limb versus lower limb) because the upper limb may respond differently to repetitive practice than the lower limb. The second comparison related to time since stroke (< 6 months versus > 6 months) because people early after stroke may respond differently to people late after stroke. The third comparison was based on dosage (≤ 24 hours versus > 24 hours of repetitive practice) because people may respond differently to higher doses of repetitive practice than lower doses. If actual dosage (frequency plus duration of therapy sessions) was reported, these data were used in preference to scheduled therapy time. The last subgroup comparison was based on initial strength (weak ie, $\leq 3/5$ MRC versus strong ie, $\geq 4/5$ MRC) since people who are weaker may respond differently to repetitive practice than those who are stronger.

All data were analysed using Review Manager software[a].

Results

Flow of studies through the review

The electronic search strategy identified 4533 studies (excluding duplicates). After screening titles, abstracts, and reference lists, 129 full reports of studies were retrieved. After inspecting the full reports, 52 studies were included. Seventy-seven studies were excluded and the reasons for exclusion are summarised in Figure 1.

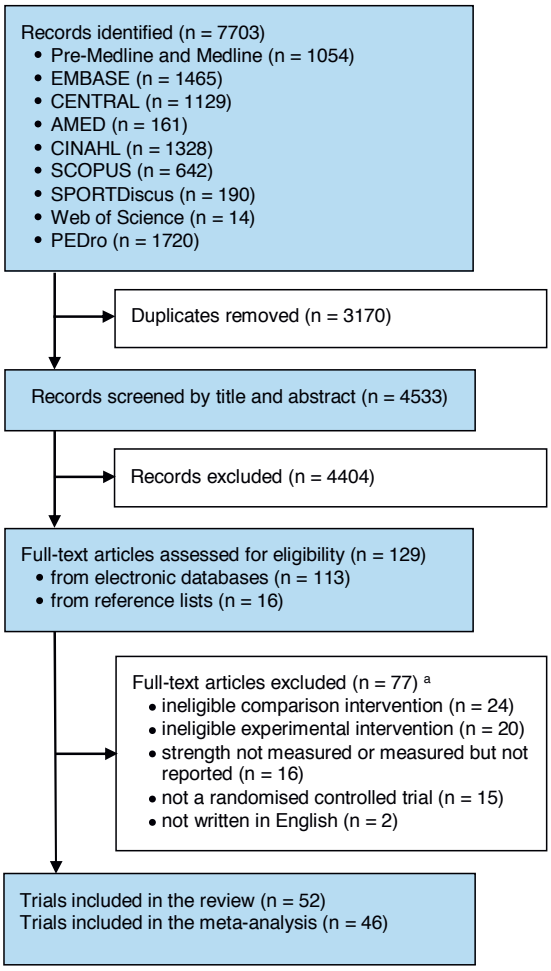

Figure 1. Flow of studies through the review.
[a] Studies may have been excluded for failing to meet more than one inclusion criterion.

Characteristics of included trials

Fifty-two studies investigated the effect of repetitive practice on strength after stroke, and some of these studies also included measures of activity (see Table 1). Additional information was requested from the authors for 15 studies[25–39] and received from eight authors.[26,29–31,33,34,38,39] Two studies met the inclusion criteria; however, strength measures were either not reported or authors were unable to provide the data.[25,40] These studies were included in the review but excluded from all meta-analyses. Four studies only reported change data for strength, and authors were unable to provide post-intervention data.[27,28,35,38] These studies were included in the review but data were analysed separately. Forty-six studies reported post-intervention data and were used to determine the overall SMD of repetitive practice on strength.

Risk of bias

The risk of bias in the 52 included studies in this systematic review was variable (see Figure 2 for details). Thirty-six studies (69%) used adequate methods for generating the randomisation sequence. Sixteen studies (31%) used adequate methods to conceal allocation. No studies were able to blind participants or therapists due to the nature of the intervention. Thirty-seven studies (71%) blinded assessors of outcomes to group allocation. Forty-three studies (83%) had complete outcome data. Forty-six studies (89%) were free of selective outcome reporting, and twelve studies (23%) were free of other bias.

Participants

The mean age of participants across the studies ranged from 47 to 79 years. The mean time since stroke ranged from 6 days to

Table 1
Characteristics of included studies (n = 52).

Study	Participants[a]	Comparison	Outcome measures[b]
Alberts (2004)[25]	n = 10/10 Exp age *(yr)* = 65 (8) Con age *(yr)* = 63 (16) Exp time since stroke *(mth)* = 6.4 (1.1) Con time since stroke *(mth)* = 5.6 (1.5)	Exp = CIMT 360 min × 5/wk × 2 wk Con = no intervention	Strength = hand grip – force *(N)* Activity = WMFT *(sec)* Endpoint: 2 wk
Almhdawi (2016)[26]	n = 20/20 Exp age *(yr)* = 61 (10) Con age *(yr)* = 63 (9) Exp time since stroke *(mth)* = 62.3 (45.2) Con time since stroke *(mth)* = 61.9 (49.4)	Exp = task-specific UL training 90 min × 2/wk × 6 wk Con = no intervention	Strength = EE – isometric force *(lb)* Activity = WMFT *(sec)* Endpoint: 7 wk
An (2016)[67]	n = 18/38 Exp age *(yr)* = 51 (10) Con age *(yr)* = 47 (11) Exp time since stroke *(mth)* = 50.6 (34.6) Con time since stroke *(mth)* = 62.7 (41.0)	Exp = weight-bearing exercise + cycling 30 min × 3/wk × 5 wk Con = no intervention Both = usual therapy	Strength = KE – isokinetic torque *(Nm/kg)* Activity = self-selected walking speed *(m/s)* Endpoint: 5 wk
Atteya (2004)[60]	n = 4/4 Exp age *(yr)* = 55 (3) Con age *(yr)* = 56 (16) Exp time since stroke *(mth)* = 5.6 (0.3) Con time since stroke *(mth)* = 4.7 (1.2)	Exp = CIMT 60 min × 3/wk × 10 wk Con = no intervention	Strength = hand grip – force *(kg)* Activity = ARAT *(/57 points)* Endpoint: 10 wk
Barker (2008)[68]	n = 23/33 Exp age *(yr)* = 67 (8) Con age *(yr)* = 69 (11) Exp time since stroke *(mth)* = 40.8 (31.2) Con time since stroke *(mth)* = 36.0 (30.0)	Exp = SMART arm training 60 min × 3/wk × 4 wk Con = no intervention	Strength = UL reaching – force *(N)* Activity = MAS *(/7 points)* Endpoint: 4 wk
Bi (2008)[41]	n = 37/77 Exp age *(yr)* = 58 (9) Con age *(yr)* = 60 (7) Exp time since stroke *(mth)* = 45.5 (30.1) Con time since stroke *(mth)* = 42.9 (34.7)	Exp = task-specific UL training + placebo-TENS 60 min × 5/wk × 8 wk Con = no intervention	Strength = hand grip – force *(N)* Activity = WMFT *(sec)* Endpoint: 8 wk
Bowman (1979)[40]	n = 30/30 Exp age *(yr)* = NR Con age *(yr)* = NR Exp time since stroke *(mth)* = NR Con time since stroke *(mth)* = NR	Exp = position-triggered FES 30 min × 2/day × 5/wk × 4 wk Con = no intervention Both = usual therapy	Strength = WE – isometric torque *(Nm)* Activity = nil Endpoint: 4 wk
Burgar (2011)[27]	n = 36/54 Exp age *(yr)* = 59 (10) Con age *(yr)* = 63 (9) Exp time since stroke *(mth)* = 0.5 (0.3) Con time since stroke *(mth)* = 0.6 (0.4)	Exp = high-dose robotic training 60 min × 30 over 3 wk Con = low-dose robotic training[c] Both = usual therapy	Strength = composite UL (14 muscle groups) – MMT *(/70 points)* Activity = WMFT *(sec)* Endpoint: 3 wk
Chan (2015)[28]	n = 25/37 Exp age *(yr)* = 56 (7) Con age *(yr)* = 59 (10) Exp time since stroke *(mth)* = 41.8 (28.7) Con time since stroke *(mth)* = 47.3 (29.8)	Exp = task-specific trunk training + placebo TENS 60 min × 5/wk × 6 wk Con = health education on measuring BP and monitoring falls[c]	Strength = TE – isometric torque *(Nm)* Activity = lateral seated reach affected *(cm)* Endpoint: 6 wk
Chu (2004)[76]	n = 12/13 Exp age *(yr)* = 62 (9) Con age *(yr)* = 63 (8) Exp time since stroke *(mth)* = 36.0 (24.0) Con time since stroke *(mth)* = 50.4 (25.2)	Exp = water-based endurance program 60 min × 3/wk × 8 wk Con = arm function program[c]	Strength = composite LL (HF/HE/KF/KE) – isokinetic torque *(Nm/kg)* Activity = self-selected walking speed *(m/s)* Endpoint: 8 wk
Cooke (2010)[29]	n = 54/109 Exp age *(yr)* = 71 (11) Con age *(yr)* = 66 (14) Exp time since stroke *(mth)* = 1.1 (0.5) Con time since stroke *(mth)* = 1.2 (0.7)	Exp = functional strength training 60 min × 4/wk × 6 wk Con = no intervention Both = usual therapy	Strength = KE – isokinetic torque *(Nm)* Activity = walking speed *(m/s)* Endpoint: 6 wk
Cowles (2013)[42]	n = 22/29 Exp age *(yr)* = 79 (8) Con age *(yr)* = 76 (12) Exp time since stroke *(mth)* = 0.6 (0.2) Con time since stroke *(mth)* = 0.6 (0.2)	Exp = observation-to-imitate + physical practice 60 min × 5/wk × 3 wk Con = no intervention Both = usual therapy	Strength = UL – Motricity Index *(/100 points)* Activity = ARAT *(/57 points)* Endpoint: 3 wk
de Sousa (2016)[52]	n = 39/40 Exp age *(yr)* = 62 (15) Con age *(yr)* = 60 (16) Exp time since stroke *(mth)* = 1.4 (1.1) Con time since stroke *(mth)* = 1.7 (1.4)	Exp = FES cycling 17 to 32 min × 5/wk × 4 wk Con = no intervention Both = usual therapy	Strength = KE – isometric torque *(Nm)* Activity = FIM – mobility *(/21 points)* Endpoint: 4 wk
Dean (2000)[43]	n = 9/12 Exp age *(yr)* = 66 (8) Con age *(yr)* = 62 (7) Exp time since stroke *(mth)* = 27.6 (8.4) Con time since stroke *(mth)* = 15.6 (10.8)	Exp = UL exercise class 60 min × 3/wk × 4 wk Con = lower limb exercise class[c]	Strength = hand grip – force *(kg)* Activity = Unimanual Purdue Pegboard *(no. of pegs)* Endpoint: 4 wk

Table 1 (*Continued*)

Study	Participants[a]	Comparison	Outcome measures[b]
Dean (2012)[44]	n = 133/151 Exp age *(yr)* = 67 (14) Con age *(yr)* = 68 (10) Exp time since stroke *(mth)* = 80.4 (80.4) Con time since stroke *(mth)* = 62.4 (64.8)	Exp = LL exercise class 45 min × 40 over 52 wk Con = upper limb exercise class[c]	Strength = KE – isometric force *(kg)* Activity = fast walking speed *(m/s)* Endpoint: 52 wk
Donaldson (2009)[30]	n = 18/30 Exp age *(yr)* = 73 (12) Con age *(yr)* = 73 (15) Exp time since stroke *(mth)* = 0.7 (0.6) Con time since stroke *(mth)* = 0.4 (0.2)	Exp = functional strength training 60 min × 4/wk × 6 wk Con = no intervention Both = usual therapy	Strength = EE – isometric force *(N)* Activity = ARAT *(/57 points)* Endpoint: 6 wk
Dorsch (2014)[53]	n = 33/33 Exp age *(yr)* = 66 (12) Con age *(yr)* = 69 (13) Exp time since stroke *(mth)* = 0.5 (0.2) Con time since stroke *(mth)* = 0.6 (0.2)	Exp = EMG-triggered FES 4 UL muscle groups × 30 reps × 5/wk × 4 wk Con = no intervention Both = usual therapy	Strength = composite UL (SF/EE/WE/TA) – MMT *(/20 points)* Activity = MAS *(/19 points)* Endpoint: 4 wk
GAPS (2004)[62]	n = 65/70 Exp age *(yr)* = 68 (11) Con age *(yr)* = 67 (10) Exp time since stroke *(mth)* = 0.7 (0.5) Con time since stroke *(mth)* = 0.8 (0.6)	Exp = additional physiotherapy 60 to 80 min × 5/wk (duration NR) Con = no intervention Both = usual therapy	Strength = composite (UL/LL) – MI *(/200 points)* Activity = RMI *(/15 points)* Endpoint: 12 wk
Gordon (2013)[45]	n = 116/128 Exp age *(yr)* = 63 (9) Con age *(yr)* = 65 (11) Exp time since stroke *(mth)* = 12.8 (3.6) Con time since stroke *(mth)* = 11.8 (3.6)	Exp = overground walking 15 to 30 min × 3/wk × 12 wk Con = massage[c]	Strength = LL – Motricity Index *(/100 points)* Activity = 6MWT *(m)* Endpoint: 12 wk
Harris (2009)[46]	n = 103/103 Exp age *(yr)* = 69 (12) Con age *(yr)* = 69 (15) Exp time since stroke *(mth)* = 0.7 (0.2) Con time since stroke *(mth)* = 0.7 (0.2)	Exp = GRASP 60 min × 6/wk × 4 wk Con = education book on stroke recovery and general health[c] Both = usual therapy	Strength = hand grip – force *(kg)* Activity = ARAT *(/57 points)* Endpoint: 4 wk
Heckmann (1997)[54]	n = 28/28 Exp age *(yr)* = 50 (14) Con age *(yr)* = 54 (11) Exp time since stroke *(mth)* = 1.8 (0.8) Con time since stroke *(mth)* = 2.0 (1.3)	Exp = EMG-triggered FES 4 UL/LL muscle groups × 15 reps × 5/wk × 4 wk Con = no intervention Both = usual therapy	Strength = DF – MMT *(/6 points)* Activity = BI *(/100 points)* Endpoint: 4 wk
Higgins (2006)[47]	n = 91/91 Exp age *(yr)* = 73 (8) Con age *(yr)* = 71 (12) Exp time since stroke *(mth)* = 7.1 (2.4) Con time since stroke *(mth)* = 7.9 (2.7)	Exp = task-specific UL training ≈ 90 min × 3/wk × 6 wk Con = walking training[c]	Strength = hand grip – force *(kg)* Activity = Box and Block *(no. of blocks)* Endpoint: 6 wk
Hsieh (2011)[57]	n = 12/18 Exp age *(yr)* = 56 (14) Con age *(yr)* = 52 (2) Exp time since stroke *(mth)* = 21.3 (7.2) Con time since stroke *(mth)* = 13.0 (7.0)	Exp = high-intensity robotic training 90 to 105 min × 5/wk × 4 wk Con = low-intensity robotic training[c]	Strength = average UL (eight muscle groups) – MMT *(/48 points)* Activity = FMA (UL) *(/66 points)* Endpoint: 4 wk
Hsieh (2012)[31]	n = 36/54 Exp age *(yr)* = 57 (10) Con age *(yr)* = 52 (12) Exp time since stroke *(mth)* = 28.7 (13.7) Con time since stroke *(mth)* = 23.3 (15.4)	Exp = high-intensity robotic training 90 to 105 min × 5/wk × 4 wk Con = low-intensity robotic training[c]	Strength = UL – MMT *(/6 points)* Activity = FMA (UL) *(/66 points)* Endpoint: 4 wk
Hwang (2012)[58]	n = 15/17 Exp age *(yr)* = 50 (4) Con age *(yr)* = 51 (3) Exp time since stroke *(mth)* = 7.3 (6.3) Con time since stroke *(mth)* = 5.3 (5.9)	Exp = active robotic hand training 40 min x 5/wk × 4 wk Con = passive/active robotic hand training[c]	Strength = hand grip – force *(kg)* Activity = Jebsen Taylor Test *(sec)* Endpoint: 4 wk
Kim (2015)[74]	n = 19/29 Exp age *(yr)* = 58 (8) Con age *(yr)* = 62 (1) Exp time since stroke *(mth)* = 10.1 (5.6) Con time since stroke *(mth)* = 13.7 (7.1)	Exp = mirror therapy + BF-FES 30 min × 5/wk × 4 wk Con = no intervention Both = usual therapy	Strength = hand grip – force *(kg)* Activity = Jebsen Taylor Test *(sec)* Endpoint: 4 wk
Kwakkel (1999)[32 d] Cooke (2010)[78]	n = 60/101 Exp age *(yr)* = 65 (10) Con age *(yr)* = 64 (15) Exp time since stroke *(mth)* = 0.2 (0.1) Con time since stroke *(mth)* = 0.2 (0.1)	Exp = task-specific LL training 30 min × 5/wk × 20 wk Con = immobilisation of LL[c] Both = usual therapy	Strength = LL – Motricity Index *(/100 points)* Activity = fast walking speed *(m/s)* Endpoint: 20 wk
Lannin (2016)[69]	n = 9/9 Exp age *(yr)* = 63 (10) Con age *(yr)* = 51 (21) Exp time since stroke *(mth)* = 2.5 (1.7) Con time since stroke *(mth)* = 4.7 (6.1)	Exp = Saebo-Flex 45 min × 5/wk × 8 wk Con = no intervention Both = usual therapy	Strength = hand grip – force *(kg)* Activity = Box and Block *(no. of blocks)* Endpoint: 8 wk
Lee (2008)[65]	n = 24/52 Exp age *(yr)* = 67 (11) Con age *(yr)* = 65 (6) Exp time since stroke *(mth)* = 52.4 (2.2) Con time since stroke *(mth)* = 65.8 (42.3)	Exp = cycling 30 min × 3/wk × 10 to 12 wk Con = sham cycling[c] Both = sham PRT	Strength = composite LL (HE/KE/KF/PF/DF) – isometric force *(N)* Activity = fast walking speed *(m/s)* Endpoint: 12 wk

Table 1 (*Continued*)

Study	Participants[a]	Comparison	Outcome measures[b]
Lee (2012)[71]	n = 40/40 Exp age *(yr)* = 54 (11) Con age *(yr)* = 54 (11) Exp time since stroke *(mth)* = 13.3 (5.9) Con time since stroke *(mth)* = 14.0 (6.3)	Exp = standing balance training (video games) 20 min × 5/wk × 4 wk Con = no intervention Both = usual therapy	Strength = KE – MMT *(/6 points)* Activity = walking speed *(s)* Endpoint: 4 wk
Lee (2013)[70]	n = 14/14 Exp age *(yr)* = 72 (9) Con age *(yr)* = 76 (6) Exp time since stroke *(mth)* = 7.3 (1.4) Con time since stroke *(mth)* = 8.3 (3.4)	Exp = UL therapy (video games) 30 min × 3/wk × 6 wk Con = no intervention Both = usual therapy	Strength = EE – MMT *(/10 points)* Activity = FIM (scale NR) Endpoint: 6 wk
Lee (2016)[75]	n = 27/30 Exp age *(yr)* = 56 (7) Con age *(yr)* = 54 (6) Exp time since stroke *(mth)* = 36.8 (26.1) Con time since stroke *(mth)* = 42.5 (33.9)	Exp = mirror therapy + FES 5/wk × 4 wk Con = no intervention Both = usual therapy	Strength = DF – isometric force *(lb)* Activity = 6MWT *(sec)* Endpoint: 4 wk
Lincoln (1999)[63]	n = 189/282 Exp age *(yr)* = 73 (12) Con age *(yr)* = 73 (12) Exp time since stroke *(mth)* = 0.4 (0.2) Con time since stroke *(mth)* = 0.4 (0.2)	Exp = additional physiotherapy ≈ 2 hrs/wk × 5 wk Con = no intervention Both = usual therapy	Strength = hand grip – force *(% of unaffected UL)* Activity = ARAT *(/57 points)* Endpoint: 5 wk
Masiero (2007)[33]	n = 30/35 Exp age *(yr)* = 63 (12) Con age *(yr)* = 69 (11) Exp time since stroke *(mth)* = NR Con time since stroke *(mth)* = NR	Exp = robotic UL training 20 to 30 min × 2/day × 5/wk × 5 wk Con = unaffected UL exposed to robot[c] Both = usual therapy	Strength = ShAbd – MMT *(/6 points)* Activity = FIM motor *(/79 points)* Endpoint: 5 wk
Ng (2007)[48]	n = 40/88 Exp age *(yr)* = 57 (8) Con age *(yr)* = 57 (9) Exp time since stroke *(mth)* = 56.4 (49.2) Con time since stroke *(mth)* = 62.4 (34.8)	Exp = task-specific LL training + placebo-TENS 60 min × 5/wk × 4 wk Con = no intervention	Strength = PF – isometric torque *(Nm)* Activity = self-selected walking speed *(cm/s)* Endpoint: 4 wk
Pang (2005)[34]	n = 60/63 Exp age *(yr)* = 66 (9) Con age *(yr)* = 65 (8) Exp time since stroke *(mth)* = 62.4 (60.0) Con time since stroke *(mth)* = 61.2 (43.2)	Exp = FAME program 60 min x 3/wk × 19 wk Con = seated UL program[c]	Strength = KE – isometric force *(N)* Activity = 6MWT *(m)* Endpoint: 19 wk
Rodgers (2003)[64]	n = 105/123 Exp age *(yr)* = 74 (NR) Con age *(yr)* = 75 (NR) Exp time since stroke *(mth)* = 0.2 (0.1) Con time since stroke *(mth)* = 0.2 (0.1)	Exp = additional physiotherapy 30 min × 5/wk × 6 wk Con = no intervention Both = usual therapy	Strength = UL – Motricity Index *(/100 points)* Activity = ARAT *(/57 points)* Endpoint: 3 mth
Ross (2009)[49]	n = 37/40 Exp age *(yr)* = 60 (21) Con age *(yr)* = 59 (19) Exp time since stroke *(mth)* = 2.3 (2.7) Con time since stroke *(mth)* = 0.7 (2.0)	Exp = task-specific UL training 60 min × 5/wk × 6 wk Con = no intervention Both = usual therapy	Strength = composite UL (nine muscle groups) – MMT *(/45 points)* Activity = ARAT *(/57 points)* Endpoint: 6 wk
Rydwik (2006)[59]	n = 9/18 Exp age *(yr)* = 75 (9) Con age *(yr)* = 75 (5) Exp time since stroke *(mth)* = 42.6 (18.2) Con time since stroke *(mth)* = 54.9 (20.0)	Exp = Stimulo robotic therapy 30 min × 3/wk × 6 wk Con = no intervention	Strength = PF – torque *(Nm)* Activity = fast walking speed *(m/s)* Endpoint: 6 wk
Sanchez-Sanchez (2016)[50]	n = 15/15 Exp age *(yr)* = 58 (12) Con age *(yr)* = 62 (11) Exp time since stroke *(mth)* = 41.3 (34.3) Con time since stroke *(mth)* = 33.8 (26.3)	Exp = UL exercise program 75 min × 33 over 12 wk Con = LL exercise program[c]	Strength = hand grip – force *(kg)* Activity = WMFT – average functional score *(/6 points)* Endpoint: 12 wk
Shin (2008)[55]	n = 14/14 Exp age *(yr)* = 61 (8) Con age *(yr)* = 54 (4) Exp time since stroke *(mth)* = 18.6 (4.2) Con time since stroke *(mth)* = 19.7 (7.7)	Exp = EMG-triggered FES 30 min × 2/day × 5/wk × 10 wk Con = no intervention Both = usual therapy	Strength = isometric MPJ extension force *(kg)* Activity = Box and Block *(no. of blocks)* Endpoint: 10 wk
Sullivan et al (2007)[35]	n = 36/80 Exp age *(yr)* = 58 (15) Con age *(yr)* = 63 (9) Exp time since stroke *(mth)* = 23.1 (15.0) Con time since stroke *(mth)* = 28.4 (19.0)	Exp = BWSTT 60 min × 4/wk × 6 wk Con = UL ergometry[c] Both = cycling	Strength = composite LL (HE, KE, PF) – isometric torque *(Nm)* Activity = fast walking speed *(m/s)* Endpoint: 6 wk
Sunderland (1992)[36]	n = 61/132 Exp age *(yr)* = 67 (NR) Con age *(yr)* = 70 (NR) Exp time since stroke *(mth)* = 0.3 (NR) Con time since stroke *(mth)* = 0.3 (NR)	Exp = additional physiotherapy Intervention period = NR Con = no intervention Both = usual therapy	Strength = UL – Extended Motricity Index (scale NR) Activity = Frenchay Arm Test *(/5 pass or fail)* Endpoint: 4 wk
Tankisheva (2014)[72]	n = 13/15 Exp age *(yr)* = 57 (13) Con age *(yr)* = 65 (4) Exp time since stroke *(mth)* = 92.5 (103.2) Con time since stroke *(mth)* = 63.4 (43.2)	Exp = whole body vibration training 30 min × 3/wk × 6 wk Con = no intervention	Strength = KE – isometric torque *(Nm)* Activity = Sensory Organisation Test (condition 6) Endpoint: 6 wk

Table 1 (*Continued*)

Study	Participants[a]	Comparison	Outcome measures[b]
Tian (2007)[66]	n = 80/80 Exp age *(yr)* = 58 (NR) Con age *(yr)* = 58 (NR) Exp time since stroke *(mth)* = NR Con time since stroke *(mth)* = NR	Exp = THERA-vital cycling 30 min × 6/wk × 4 wk Con = no intervention Both = usual therapy	Strength = LL – MMT *(/6 points)* Activity = ADL *(/8 grades)* Endpoint: 4 wk
Tihanyi (2010)[73]	n = 20/20 Exp age *(yr)* = 58 (5) Con age *(yr)* = 58 (8) Exp time since stroke *(mth)* = 0.9 (0.3) Con time since stroke *(mth)* = 0.8 (0.3)	Exp = whole body vibration training 3/wk × 4 wk Con = no intervention Both = usual therapy	Strength = KE – isometric torque *(Nm)* Activity = nil Endpoint: 4 wk
Tung (2010)[37]	n = 32/32 Exp age *(yr)* = 51 (21) Con age *(yr)* = 53 (14) Exp time since stroke *(mth)* = 26.9 (16.0) Con time since stroke *(mth)* = 12.8 (12.3)	Exp = STS training 15 min × 3/wk × 4 wk Con = no intervention Both = usual therapy	Strength = KE – force *(% normalised to body-weight)* Activity = Berg Balance Scale *(/56 points)* Endpoint: 4 wk
Tyson (2015)[38]	n = 85/94 Exp age *(yr)* = 64 (15) Con age *(yr)* = 64 (13) Exp time since stroke *(mth)* = 0.9 (0.6) Con time since stroke *(mth)* = 1.2 (0.9)	Exp = patient-led mirror therapy 30 min × 7/wk × 4 wk Con = patient-led LL exercise[c] Both = usual therapy	Strength = hand grip – force (units NR) Activity = ARAT *(/57 points)* Endpoint: 4 wk
Winchester (1983)[56]	n = 40/40 Exp age *(yr)* = 57 (13) Con age *(yr)* = 60 (10) Exp time since stroke *(mth)* = 1.5 (1.2) Con time since stroke *(mth)* = 1.9 (1.3)	Exp = position-triggered FES + ES 30 min × 5/wk × 4 wk Con = no intervention Both = usual therapy	Strength = KE – isometric torque *(Nm)* Activity = nil Endpoint: 4 wk
Winstein (2004)[39]	n = 40/64 Exp age *(yr)* = 58 (10) Con age *(yr)* = 50 (10) Exp time since stroke *(mth)* = 0.5 (0.2) Con time since stroke *(mth)* = 0.5 (0.2)	Exp = task-specific UL training 60 min × 5/wk × 4 wk Con = no intervention Both = usual therapy	Strength = composite UL (ShE, ShF, EE, EF, WE, WF) – isometric torque *(kg/cm)* Activity = FTHUE *(/18 points)* Endpoint: 4 to 6 wk
Yang (2006)[51]	n = 48/48 Exp age *(yr)* = 57 (10) Con age *(yr)* = 60 (10) Exp time since stroke *(mth)* = 62.7 (27.4) Con time since stroke *(mth)* = 64 (40.4)	Exp = task-specific strength training 30 min × 3/wk × 4 wk Con = no intervention	Strength = KE – isometric force *(lb)* Activity = self-selected walking speed *(cm/s)* Endpoint: 4 wk
Yoon (2014)[61]	n = 18/26 Exp age *(yr)* = 64 (9) Con age *(yr)* = 61 (17) Exp time since stroke *(mth)* = 0.6 (0.3) Con time since stroke *(mth)* = 0.8 (0.4)	Exp = CIMT 360 min × 5/wk × 2 wk Con = independent exercise program[c] Both = usual therapy + independent exercise program	Strength = hand grip – force *(kg)* Activity = WMFT *(sec)* Endpoint: 2 wk

ARAT = Action Research Arm Test, ADL = activities of daily living, BI = Barthel Index, BP = blood pressure, BWSTT = body-weight-supported treadmill training, CIMT = constraint-induced movement therapy, Con = control group, DF = dorsiflexors, EE = elbow extensors, EF = elbow flexors, EMG = electromyography, ES = electrical stimulation, Exp = experimental group, FAME = Fitness and Mobility Exercise, FES = Functional Electrical Stimulation, FMA = Fugl-Meyer Assessment, FTHUE = Functional Test for the Hemiparetic Upper Extremity, GRASP = Graded Repetitive Arm Supplementary Program, HAbd = hip abductors, HE = hip extensors, HF = hip flexors, KE = knee extensors, KF = knee flexors, LL = lower limb, MAS = Motor Assessment Scale, MI = Motricity Index, MMT = Manual Muscle Test, MPJ = metacarpophalangeal joint, NR = not reported, PF = plantarflexors, RM = repetition maximum, RMI = Rivermead Mobility Index, ShAbd = shoulder abductors, ShAdd = shoulder adductors, ShE = shoulder extensors, ShER = shoulder external rotators, ShF = shoulder flexors, ShIR = shoulder internal rotators, TA = thumb abductors, TE = trunk extension, TENS = transcutaneous electrical nerve stimulation, UL = upper limb, WE = wrist extensors, WF = wrist flexors, WMFT = Wolf Motor Function Test.

[a] n = number of participants analysed/number of participants randomised. Age *(yr)* and time since stroke *(mth)* = mean (SD).

[b] Outcome measures and endpoint used in data analysis.

[c] Considered to be equivalent to no intervention or of lower dosage when compared with the experimental group.

[d] Data obtained from Kwakkel (1999) and Cooke et al (2010).

8 years, with 28 of the 52 studies including participants who were more than 6 months after their stroke.

Intervention

The experimental intervention, repetitive practice, was provided in the following ways: task-specific training[26,28–30,32,34,35,37,39,41–51] (provided in a group setting or on a one-to-one basis) (20 studies); electromyography-triggered functional electrical stimulation (FES) or FES combined with active movement[40,52–56] (six studies); robotics[27,31,33,57–59] (six studies); constraint-induced movement therapy[25,60,61] (three studies); Bobath[62–64] (three studies); cycling[65,66] (two studies); mixed therapies that included a number of interventions[36,67] (two studies); assistive technology[68,69] (SMART Arm & SAEBO) (two studies); video games[70,71] (two studies); whole body vibration combined with active movement[72,73] (two studies); mirror therapy and FES combined with active movement[74,75] (two studies); mirror therapy[38] (one study); and water-based exercise[76] (one study). The frequency and duration of therapy sessions, and intensity and progression of practice was variable (see Appendix 2 on the eAddenda). The duration of therapy sessions ranged from 15 to 360 minutes including rest breaks. Overall average dosage (frequency plus duration of therapy sessions) ranged from 2.2 hours over 4 weeks to 60 hours over 2 weeks. Sixteen studies reported total repetitions of active practice ranging from five repetitions per exercise to 1800 repetitions per therapy session. These repetitions were counted throughout a session or specified prior to each therapy session. Thirty-three studies compared repetitive practice to no intervention[25,26,29,30,36,37,39–42,48,49,51–56,59,60,62–64,66–75] and 19 studies compared repetitive practice to a sham intervention.[27,28,31–35,38,43–47,50,57,58,61,65,76]

Outcome measures

Strength of the affected upper or lower limb was measured in the following ways: maximum force[25,26,30,34,38,41,43,44,46,47,50,51,55,58,60,61,65,68,69,74,75] (21 studies); torque[28,29,35,39,40,48,52,56,59,67,72,73,76] (13 studies); Motricity Index[32,42,45,62,64] (five studies); Extended Motricity Index[36] (one study); manual muscle testing[27,31,33,49,53,54,57,66,70,71] (10 studies); and percentage of strength normalised to body-weight[37] or expressed as a percentage of the unaffected side[63] (two studies).

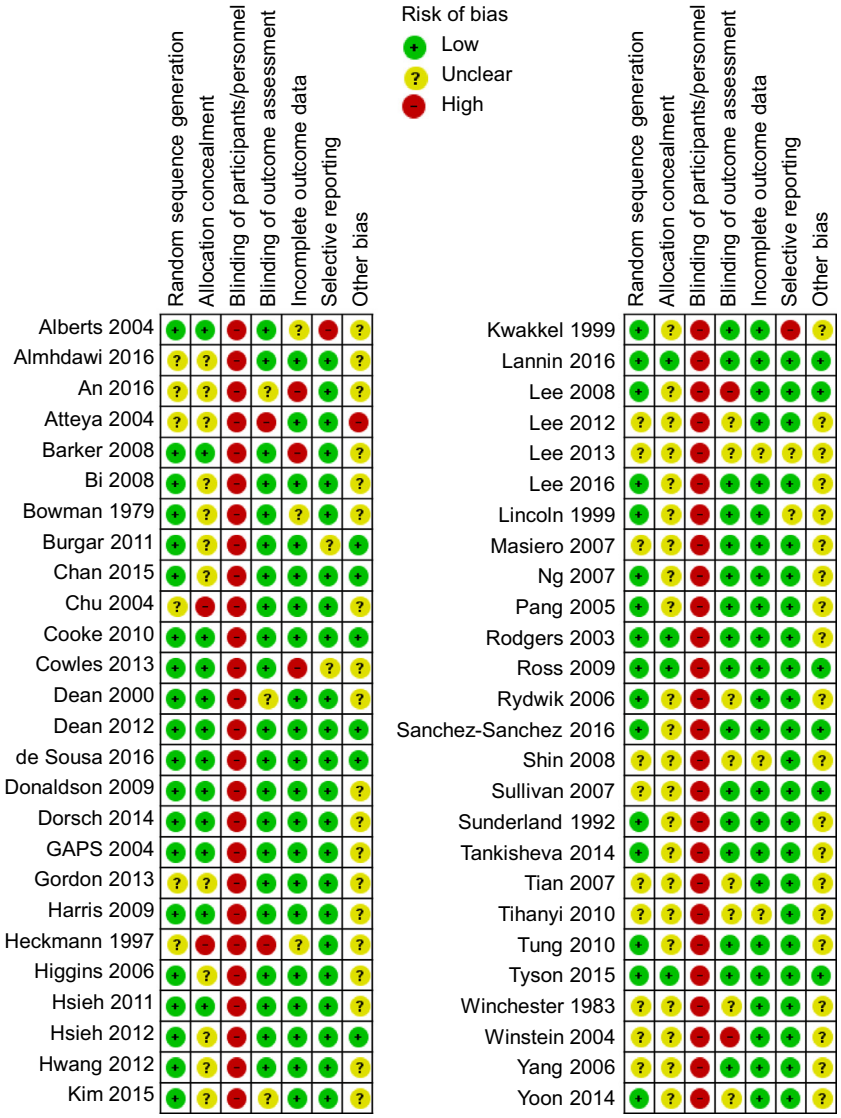

Figure 2. The risk of bias in the included studies (n = 52).
Green = low risk of bias, yellow = unclear risk of bias, red = high risk of bias.

Activity of the upper and lower limb was measured using various scales (see Appendix 3 on the eAddenda).

Effects of repetitive practice

Strength

Forty-six studies with a total of 1928 participants investigated the effects of repetitive practice on strength after stroke. The overall SMD of repetitive practice on strength when the upper and lower limb studies were combined was 0.25 (95% CI 0.16 to 0.34, I^2 = 44%) in favour of repetitive practice (Figure 3, see Figure 4 on the eAddenda for a detailed forest plot). These studies involved 12 different types of interventions that were analysed in separate meta-analyses. The most common intervention was task-specific training, with 18 studies and a total of 931 participants. The SMD was 0.21 (95% CI 0.08 to 0.34, I^2 = 36%) in favour of task-specific training on strength. The intervention with the largest effect on strength was constraint-induced movement therapy, with two studies and a total of 22 participants. The SMD was 1.49 (95% CI 0.44 to 2.54, I^2 = 57%) in favour of constraint-induced movement therapy on strength. The intervention with the next largest effect on strength was assistive technology, with two studies and a total of 32 participants. The SMD was 1.02 (95% CI 0.26 to 1.78, I^2 = 29%) in favour of assistive technology on strength. Four studies[27,28,35,38] with a total of 182 participants only reported change data for strength; however, statistical heterogeneity was too high to pool results in a meta-analysis.

Upper limb activity

Twenty-four studies with a total of 912 participants investigated the effects of repetitive practice on upper limb activity after stroke. The SMD was 0.15 (95% CI 0.02 to 0.29, I^2 = 50%) in favour of repetitive practice on upper limb activity (Figure 5, see Figure 6 on the eAddenda for a detailed forest plot). This translates to an absolute mean increase of 3.1/57 points (95% CI 0.4 to 5.8) on the ARAT (upper limb activity) when the results are back converted using the largest, least biased and most representative study of those included in the analysis.[46] These studies involved eight different types of interventions that were analysed in separate meta-analyses. The most common intervention involving repetitive practice was task-specific training, with 10 studies and a total of 392 participants. The SMD was 0.21 (95% CI 0.01 to 0.41, I^2 = 0%) in favour of task-specific training on upper limb activity. Two studies[27,38] with a total of 121 participants only reported change data for upper limb activity after stroke. The SMD was –0.12 (95% CI –0.50 to 0.25, I^2 = 0%) in favour of no intervention or a sham intervention.

Lower limb activity

Twenty studies with a total of 952 participants investigated the effects of repetitive practice on lower limb activity after stroke. The SMD was 0.25 (95% CI 0.12 to 0.38, I^2 = 36%) in favour of repetitive practice on lower limb activity (Figure 7, see Figure 8 on the eAddenda for a detailed forest plot). This translates to an absolute mean increase of 0.13 m/s (95% CI 0.06 to 0.20) in walking speed

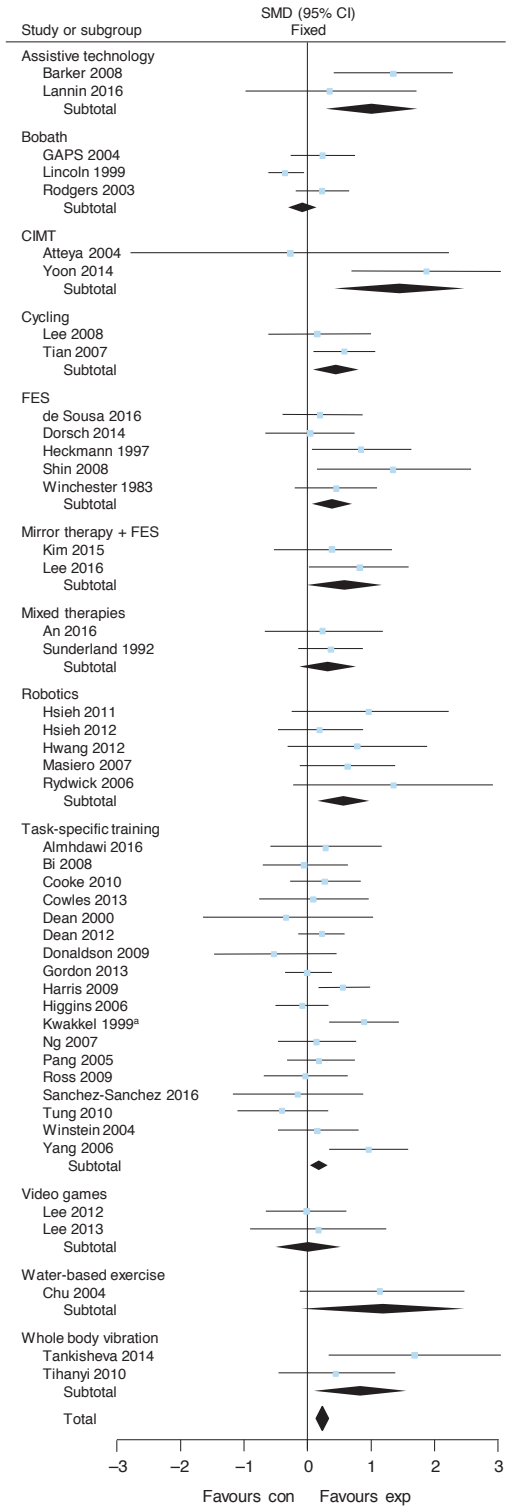

Figure 3. The effect of repetitive practice versus no intervention or sham on strength (n = 1928).
Effects are expressed as SMD (95% CI).
[a] Means (SD) obtained from Cooke et al 2010.

when the results are back converted using the largest, least biased and most representative study of those included in the analysis.[44] These studies involved 10 different types of interventions that were analysed in separate meta-analyses. The most common intervention involving repetitive practice was task-specific training, with nine studies and a total of 593 participants. The SMD was 0.32 (95% CI 0.16 to 0.48, I^2 = 35%) in favour of task-specific training on lower limb activity. One study with a total of 25 participants only reported change data for lower limb activity after stroke.[28] The MD in lateral seated reach to the affected side was 4.30 cm (95% CI 1.57 to 7.03) in favour of repetitive practice on lower limb activity.

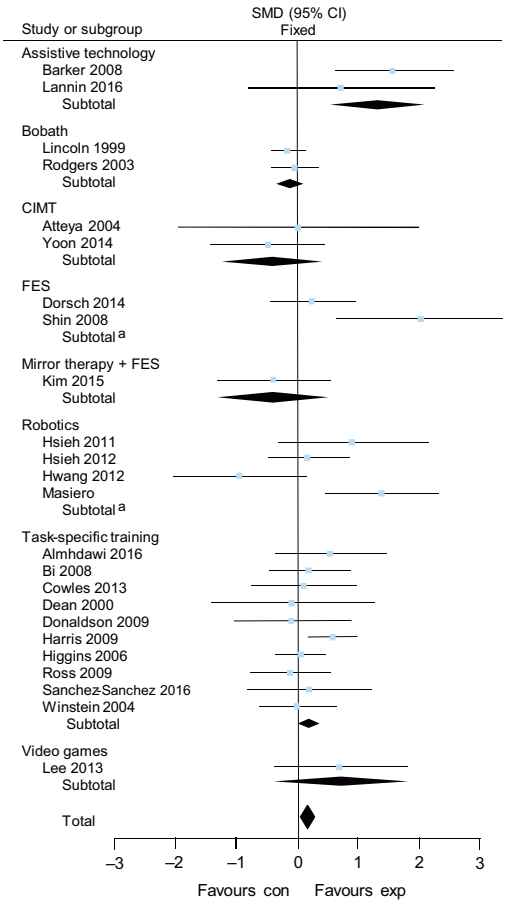

Figure 5. The effect of repetitive practice versus no intervention or sham on upper limb activity (n = 912).
Effects are expressed as SMD (95% CI).
A negative time score reflects improvement in speed on the Wolf Motor Function Test and Jebsen Taylor Test.
[a] No subtotals are presented for FES or Robotics because the I^2 value was > 75%.

Subgroup analyses

When studies were grouped according to upper and lower limb, there were 25 studies with a total of 973 participants that investigated the effects of repetitive practice on upper limb strength and 21 studies with a total of 955 participants that investigated the effects of repetitive practice on lower limb strength. The SMD was 0.16 (95% CI 0.03 to 0.29, I^2 = 47%) in favour of repetitive practice on upper limb strength and 0.34 (95% CI 0.22 to 0.47, I^2 = 34%) in favour of repetitive practice on lower limb strength (see Figures 9 and 10 on the eAddenda for the detailed forest plots). This translates to an absolute mean increase of 1.28 kg (95% CI 0.24 to 2.32) in hand grip strength and 5.75 Nm (95% CI 3.72 to 7.94) in knee extensor strength when the results are back converted using the largest, least biased, and most representative study of those included in the analysis.[29,46]

When the studies were grouped according to time after stroke, there were 21 studies with a total of 1054 participants that investigated the effects of repetitive practice on strength early after stroke and 25 studies with a total of 874 participants that examined the effects of repetitive practice on strength late after stroke. The SMD was 0.32 (95% CI 0.13 to 0.52, I^2 = 53%) in favour of repetitive practice early after stroke and 0.31 (95% CI 0.13 to 0.49, I^2 = 36%) in favour of repetitive practice late after stroke.

When studies were grouped according to dosage, there were 35 studies with a total of 1572 participants that provided repetitive practice for a total of ≤ 24 hours, and 11 studies with a total of 356 participants that provided repetitive practice for a total of > 24 hours. The SMD was 0.24 (95% CI 0.14 to 0.34, I^2 = 41%) in favour of repetitive practice provided for a total of ≤ 24 hours and 0.31 (95% CI 0.10 to 0.53, I^2 = 53%) in favour of repetitive practice provided for a total of > 24 hours.

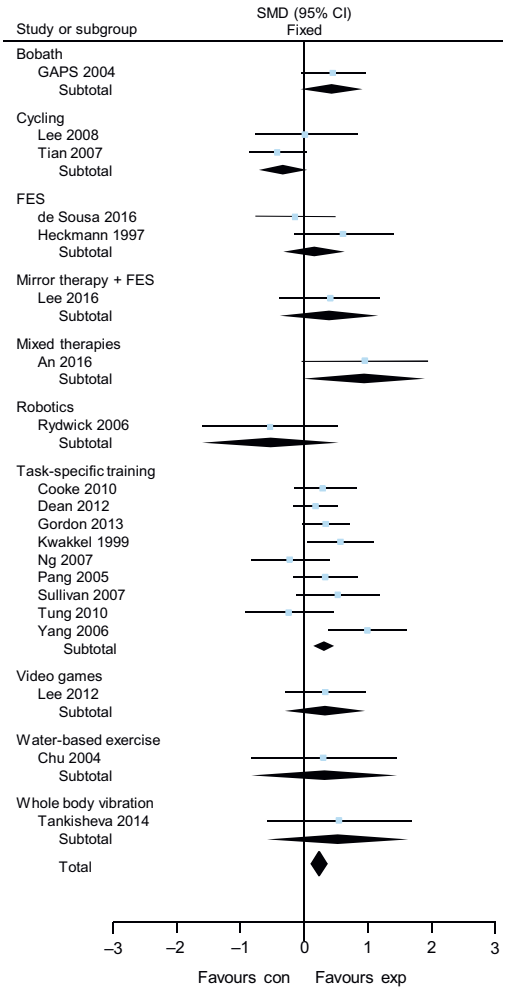

Figure 7. The effect of repetitive practice versus no intervention or sham on lower limb activity (n = 952).
Effects are expressed as SMD (95% CI).
A negative time score reflects improvement in walking speed on the 6-m and 10-m walk tests.

A subgroup analysis was planned for the effects of repetitive practice on strength in people who are weaker versus people who are stronger; however, because most studies recruited both weaker and stronger participants, this analysis was not possible.

Post-hoc analysis

When studies were grouped according to limbs that were trained and time since stroke, there were 13 studies with a total of 668 participants that investigated the effects of repetitive practice on upper limb strength early after stroke, and 12 studies with 305 participants that investigated the effects of repetitive practice on upper limb strength late after stroke. The SMD was 0.22 (95% CI –0.06 to 0.49, I^2 = 59%) in favour of repetitive practice on upper limb strength early after stroke and 0.23 (95% CI 0.00 to 0.46, I^2 = 29%) in favour of repetitive practice on upper limb strength late after stroke. There were eight studies with a total of 386 participants that investigated the effects of repetitive practice on lower limb strength early after stroke and 13 studies with a total of 569 participants that investigated the effects of repetitive practice on lower limb strength late after stroke. The SMD was 0.48 (95% CI 0.28 to 0.69, I^2 = 0%) in favour of repetitive practice on lower limb strength early after stroke and 0.25 (95% CI 0.08 to 0.42, I^2 = 45%) in favour of repetitive practice on lower limb strength late after stroke (see Appendix 4 on the eAddenda).

Sensitivity analysis

Sensitivity analyses were conducted on the primary meta-analysis for strength to explore the effects of various methodological aspects of the included studies. The only substantial difference on the estimate for strength was found in the analysis of eight studies with a total of 343 participants that were free from other bias. The SMD was 0.19 (95% CI –0.03 to 0.40) in favour of repetitive practice (see Appendix 5 on the eAddenda). This was a smaller and less precise estimate than the overall SMD on strength when the upper and lower limb studies were combined (0.25, 95% CI 0.16 to 0.34).

Discussion

This systematic review provides evidence that interventions involving repetitive practice improve strength after stroke. The pooled mean treatment effects for upper and lower limbs are 1.28 kg and 5.75 Nm, respectively. This represents a 15% relative increase in strength in the upper limb, and a 28% relative increase in strength in the lower limb when compared to mean baseline strength. These estimates are reasonably precise with the 95% CI spanning from 0.24 to 2.32 kg (equivalent to a 3 to 26% relative increase) in the upper limb and 3.72 to 7.94 Nm (equivalent to an 18 to 39% relative increase) in the lower limb. These results suggest that the effect of repetitive practice on strength is greater in the lower limb (knee extension) than the upper limb (hand grip). These findings are similar in the post-hoc analyses that restricted studies to early after stroke. That is, the effects of repetitive practice on strength are greater in the lower limb (8.11 Nm, 95% CI 4.73 to 11.66) compared to the upper limb (1.76 kg, 95% CI –0.48 to 3.92).

These results suggest that small improvements in strength with repetitive practice translate into small improvements in activity of the upper (SMD 0.15, 95% CI 0.02 to 0.29) and lower limb (SMD 0.25, 95% CI 0.12 to 0.38) after stroke. The results for activity need to be interpreted with caution because the aim of this review was not to determine the effect of repetitive practice on activity. Instead, this was a secondary analysis used to determine whether improvements in strength were accompanied by improvements in activity. Therefore, it did not include studies that measured activity unless they measured strength. Other reviews provide the best evidence about the effects of repetitive practice on activity.[12,14,15,77] However, a unique feature of our review is that it provides insights into the possible mechanisms underlying the observed improvement in activity with repetitive practice. The accompanying improvement in activity with improvement in strength suggests that the observed improvement in activity may, at least in part, be due to improvement in strength.

Of course, not all of the observed improvements in activity can be attributed solely to improvements in strength. Repetitive practice typically involves practice of tasks, which demands the integration of strength, coordination and sensory input. Thus, improvements in strength with repetitive practice are more likely to translate into improvements in activity than interventions that involve isolated strength training of muscles (eg, progressive resistance training).

Our results suggest smaller improvements in strength with repetitive practice (SMD 0.25, 95% CI 0.16 to 0.34) than reviews of progressive resistance training (SMD 0.98, 95% CI 0.67 to 1.29)[10] and electrical stimulation (SMD 0.47, 95% CI 0.26 to 0.68).[22] However, we cannot conclude that these other interventions improve strength more than repetitive practice for two main reasons. Firstly, to answer questions about relative effectiveness, interventions need to be compared in a randomised controlled trial. Secondly, studies of progressive resistance training may not have included people who are very weak; therefore, the cohorts of the studies included in the review of progressive resistance training may be different to the cohorts of the studies in our review.

Some clinicians may disagree with our definition of repetitive practice. Repetitive practice was defined as voluntary contraction of muscles of the affected upper or lower limb, and could have included repetitive practice of a whole task or components of a task. This definition was intentionally broad because people after

stroke may be too weak to practise a whole task (eg, reaching and manipulation of objects). Therefore, repetitive practice of components of a task (eg, elbow extension and finger flexion/extension) are needed prior to, and in combination with, whole task practice.

There is some indication that an increased dosage of repetitive practice improves strength after stroke. In studies where the total dosage was $\leq$ 24 hours, the SMD was 0.24 (95% CI 0.14 to 0.34) in favour of repetitive practice. When the total dosage of repetitive practice was $>$ 24 hours, the SMD was slightly more, namely 0.31 (95% CI 0.10 to 0.53) in favour of repetitive practice. However, dosage was difficult to quantify in this review because most studies did not report actual duration of active practice, and only 16 studies reported total repetitions of active practice or specified the total amount of repetitions aimed for in each therapy session. For this reason, we were forced to rely on data about scheduled therapy time. Surprisingly, one study only provided 2.2 hours of active practice over 4 weeks (equivalent to 0.5 hour per week). At the other extreme, one study provided 60 hours of active practice over 2 weeks (equivalent to 30 hours per week). Clearly, the dose-response relationship of repetitive practice is complex and requires further investigation in large randomised controlled trials.

This review is unique because it included all randomised trials that investigated the effects of repetitive practice on strength after stroke. This review also provides individual estimates of improvements in strength for 12 different types of interventions involving repetitive practice. No other systematic review has investigated these issues. This review provides meta-analyses of the effects of repetitive practice in the upper limb both early and late after stroke, and in the lower limb both early and late after stroke. These analyses are useful because there may be differences in the way the upper and lower limbs respond to repetitive practice at different times after stroke.

The main limitation of this review was that a minimum worthwhile treatment effect for strength was not defined a priori, making it difficult to determine if a statistically significant result was clinically worthwhile. However, data were converted to relative improvements in strength to help clinicians interpret the results (see Appendices 6 and 7 on the eAddenda). Another limitation was that post-intervention data were used instead of change data. Change data may have provided a more precise estimate of effect of repetitive practice on strength. Post-intervention data were used in preference to change data because these were the most commonly provided data in studies.

The loss of strength is a common and important impairment after stroke. In addition, repetitive practice is widely used and recommended in rehabilitation after stroke to improve activity. However, prior to this review it was not known whether improvements in activity with repetitive practice are accompanied by improvements in strength. This systematic review provides evidence that interventions involving repetitive practice do improve strength after stroke, and these improvements are accompanied by improvements in activity. This suggests that repetitive practice should be prioritised as an intervention that can improve both strength and activity in people after stroke.

What was already known on this topic: Loss of strength after stroke is common, and causes profound limitations in activity and participation. Progressive resistance training can be used to increase strength after stroke but it can be time-consuming to set up and monitor.
What this study adds: Interventions involving repetitive practice improve strength after stroke, and the improvement in strength is accompanied by improvements in activity. Repetitive practice should be prioritised as an intervention that can improve both strength and activity in people after stroke.

Footnote: [a] Review Manager Version 5.3, The Nordic Cochrane Centre, Copenhagen.

eAddenda: Figures 4, 6, 8, 9 and 10, and Appendices 1, 2, 3, 4, 5, 6 and 7 can be found online at https://doi.org/10.1016/j.jphys.2018.08.004

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Correspondence: Davide G de Sousa, Graythwaite Rehabilitation Centre, Ryde Hospital, Sydney, Australia. Email: davidedesousa@gmail.com

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Websites

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Chapter 4 Functional electrical stimulation cycling does not improve mobility in people with acquired brain injury and its effects on strength are unclear: a randomised trial

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Published manuscript

This project is presented as a published manuscript:

de Sousa DG, Harvey LA, Dorsch S, Leung J, Harris W. Functional electrical stimulation cycling does not improve mobility in people with acquired brain injury and its effects on strength are unclear: a randomised trial. Journal of Physiotherapy. 2016;62(4):203-208.

Published abstract

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Conference proceedings

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

1. **de Sousa DG,** Harvey LA, Dorsch S. Does cycling with electrical stimulation (ES) improve strength and walking ability in people with an acquired brain injury? A randomised controlled trial. Smart Strokes, Brisbane, Australia, 2013.
2. **de Sousa DG,** Harvey LA, Dorsch S, Leung J, Harris W. Does functional electrical stimulation (FES) cycling improve mobility and strength in people with acquired brain injury? World Confederation for Physical Therapy Congress, Cape Town, South Africa, 2017.

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Statement from co-authors confirming the authorship contribution of the PhD candidate. As co-authors of the manuscript:

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We confirm that Davide de Sousa has made the following contributions:

- Conception and design of the research including literature search
- Collection of data
- Analysis and interpretation of the findings
- Writing the manuscript, critical appraisal of content and response to reviewers

Name	Signature	Date
Lisa Anne Harvey		30-Aug-2019
Simone Dorsch		30-Aug-2019
Joan Leung		30-Aug-2019
Whitney Harris		30-Aug-2019

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Research

Functional electrical stimulation cycling does not improve mobility in people with acquired brain injury and its effects on strength are unclear: a randomised trial

Davide G de Sousa [a,b,c], Lisa A Harvey [b,c], Simone Dorsch [d], Joan Leung [e], Whitney Harris [f]

[a] Graythwaite Rehabilitation Centre, Ryde Hospital; [b] John Walsh Centre for Rehabilitation Research, Kolling Institute, Northern Sydney Local Health District; [c] Sydney Medical School Northern, University of Sydney; [d] School of Physiotherapy, Australian Catholic University; [e] Royal Rehab, Ryde; [f] Prince of Wales Hospital, South Eastern Sydney Local Health District, Sydney, Australia

KEY WORDS

Functional electrical stimulation
Stroke
Acquired brain injury
Physical therapy
FES cycling

ABSTRACT

Question: Does 4 weeks of active functional electrical stimulation (FES) cycling in addition to usual care improve mobility and strength more than usual care alone in people with a sub-acute acquired brain injury caused by stroke or trauma? **Design:** Multi centre, randomised, controlled trial. **Participants:** Forty patients from three Sydney hospitals with recently acquired brain injury and a mean composite strength score in the affected lower limb of 7 (SD 5) out of 20 points. **Intervention:** Participants in the experimental group received an incremental, progressive, FES cycling program five times a week over a 4-week period. All participants received usual care. **Outcome measures:** Outcome measures were taken at baseline and at 4 weeks. Primary outcomes were mobility and strength of the knee extensors of the affected lower limb. Mobility was measured with three mobility items of the Functional Independence Measure and strength was measured with a hand-held dynamometer. Secondary outcomes were strength of the knee extensors of the unaffected lower limb, strength of key muscles of the affected lower limb and spasticity of the affected plantar flexors. **Results:** All but one participant completed the study. The mean between-group differences for mobility and strength of the knee extensors of the affected lower limb were −0.3/21 points (95% CI −3.2 to 2.7) and 7.5 Nm (95% CI −5.1 to 20.2), where positive values favoured the experimental group. The only secondary outcome that suggested a possible treatment effect was strength of key muscles of the affected lower limb with a mean between-group difference of 3.0/20 points (95% CI 1.3 to 4.8). **Conclusion:** Functional electrical stimulation cycling does not improve mobility in people with acquired brain injury and its effects on strength are unclear. **Trial registration:** ACTRN12612001163897. **[de Sousa DG, Harvey LA, Dorsch S, Leung J, Harris W (2016) Functional electrical stimulation cycling does not improve mobility in people with acquired brain injury and its effects on strength are unclear: a randomised controlled trial. *Journal of Physiotherapy* 62: 203–208]**

Introduction

Walking and moving around are some of the most important goals for people with acquired brain injury caused by stroke or trauma. Often, however, these goals are not achieved. For example, one estimate indicates that 40% of stroke survivors who are unable to walk on admission to rehabilitation are still unable to walk at 3 months.[1] To improve the ability to walk and move around, people with acquired brain injury require intensive repetitive practice[2,3] in combination with interventions that address impairments such as weakness.[4,5] However, many patients in rehabilitation spend only 1 hour per day with a physiotherapist and are inactive for as much as 70% of the day.[6–8] One reason for this inactivity following acquired brain injury is that those who are very immobile and weak have few options for exercising independently; they often require assistance from two or more physiotherapists, which is costly and time consuming.

Functional electrical stimulation (FES) cycling may help overcome this problem because patients can cycle without physical assistance from physiotherapists. Functional electrical stimulation cycling involves the application of a small electrical current through the skin to stimulate muscle contractions in synchrony with the pedalling motion of a lower limb ergometer. If used in addition to routine face-to-face physiotherapy, FES cycling may increase strength in the lower limbs, which may have carryover effects on the patient's ability to walk and move around.

There are two recent systematic reviews of electrical stimulation (ES) and FES on the upper and lower limbs in people with stroke.[9,10] Both indicated improvements in function, including mobility, and one also showed increases in strength. However, neither of these two reviews looked at the effect of FES cycling. There are four studies that have specifically looked at FES cycling in sub-acute hemi-paretic patients.[11–14] Two of these studies did not measure strength[13,14] or mobility,[13] and had small sample sizes ($n \leq 20$). The

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other two studies are relevant to the question of whether FES cycling has therapeutic effects. The first study suggested increases in lower limb strength but not walking,[11] and the second suggested the opposite, namely: improvements in walking but not lower limb strength.[12] It is therefore unclear whether FES cycling is therapeutic. Interestingly, in the study that showed a treatment effect on strength, participants were instructed to remain passive and not actively contribute to the cycling.[11] Remaining passive while cycling is not in keeping with current research on neural plasticity, which suggests that purposeful active movement is essential.[15,16] It would seem more likely that FES cycling would need to be combined with maximal voluntary effort from patients to see carryover effects on mobility and strength. It is worth trying to better understand whether FES cycling is potentially therapeutic because it is a relatively inexpensive intervention that does not require direct assistance from a physiotherapist.

Therefore, the research question for this multi centre, randomised, controlled trial was:

Does 4 weeks of active FES cycling in addition to usual care improve mobility and strength more than usual care alone in people with a sub-acute acquired brain injury caused by stroke or trauma?

Method

Design

An assessor-blinded, randomised, controlled trial was undertaken (Figure 1). Using computer software,[a] a person not involved in the trial created a blocked random allocation schedule for 40 participants. The blocking ensured equal numbers of participants in the two groups. Participants' allocations were placed in opaque, sequentially numbered and sealed envelopes that were held off-site by a person not otherwise involved in the trial. Once a participant passed the screening process and completed the initial assessment, trial staff contacted the independent person, who opened the next envelope and revealed the group allocation. The participant was considered to have entered the trial at this point. The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR: 12612001163897), however, one of the secondary outcomes was erroneously omitted from the trial registry, although it was included in the protocol and is reported here. The authors certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed.

Participants

All patients admitted to three sub-acute adult rehabilitation units between 11 February 2013 and 21 October 2015 were screened for inclusion. The inclusion criteria were: first time stroke or any other non-progressive acquired brain injury; hemiparesis with composite strength in the affected lower limb $< 19/20$ points; less than 6 months after acquired brain injury; ability to sit supported for 40 minutes; and sufficient communication skills to indicate yes/no verbally or via gestures. Patients were excluded for the following reasons: limited joint range of movement or a musculoskeletal condition preventing use of the lower limb cycle; cardiac pacemakers; inability to tolerate the ES; pregnancy; absence of notable contraction of lower limb muscles with ES; or unstable medical conditions.

Interventions

Participants allocated to the experimental group received an incremental progressive, individualised FES cycling program,

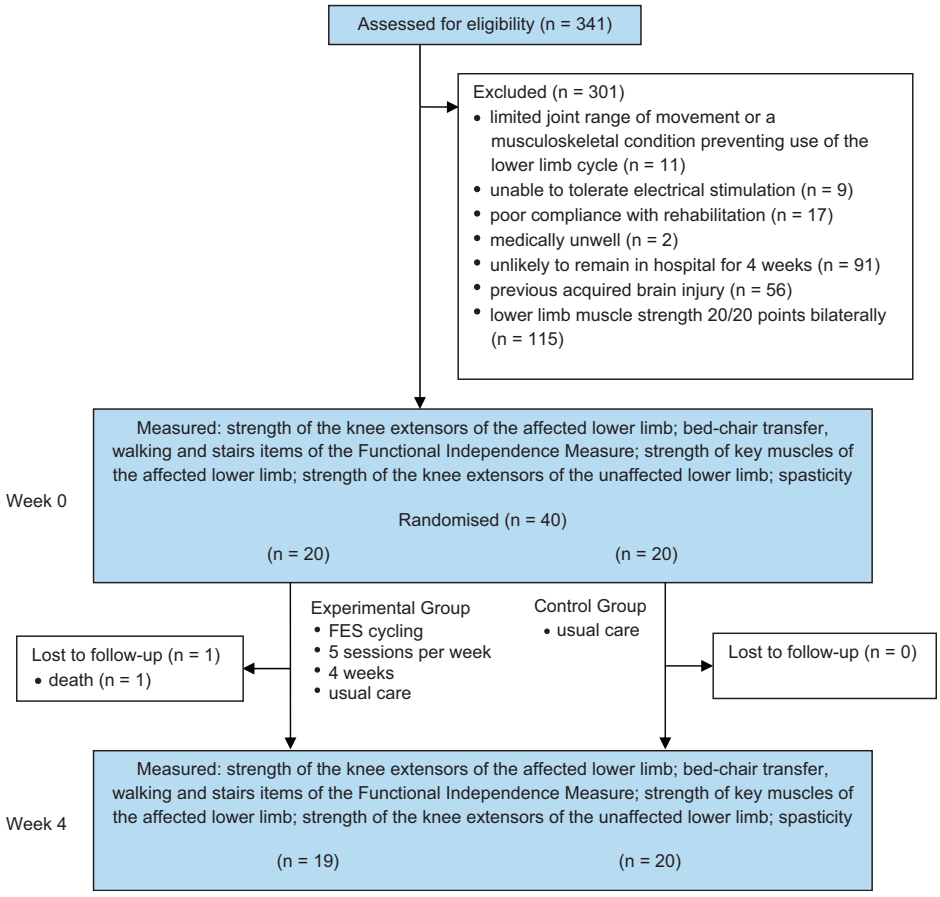

Figure 1. Flow diagram.

which was undertaken five times a week for 4 weeks. In the first week, they cycled for 17 minutes per day on a FES cycle lower limb ergometer.[b] This was increased by at least 5 minutes per week, and more if tolerated, up to a maximum of 32 minutes per day. The FES was applied through pads placed on the skin and over four muscle groups: knee extensors, knee flexors, ankle dorsiflexors and plantar flexors of the affected lower limb. Knee extensors and ankle dorsiflexors were stimulated between 35 and 56%, and knee flexors and ankle plantar flexors between 81 and 98% of one complete revolution of the FES cycle pedal. Photographs and instructions were given to the physiotherapists administering the intervention to provide general guidance on electrode placement, although physiotherapists had some freedom to slightly move the electrodes to where they achieved a strong contraction. Cycle cadence was set at 30 repetitions per minute for all participants. Frequency and wavelength was set at 50 Hz and 450 λ, respectively. The participants were instructed to actively cycle as hard as possible and in synchrony with the FES. The intensity of the FES was adjusted progressively to provide strong muscle contractions or the maximal tolerated stimulation. Resistance was increased to ensure the participants worked as hard as they could tolerate. In addition, the experimental group received usual care as provided to the control group. All participants were supervised by a physiotherapist.

The control group received usual care, which consisted of at least 1 hour a day of one-to-one therapy with a physiotherapist. This therapy involved strength, endurance, balance and coordination exercises, as well as task-specific practice of sitting, sitting-to-standing, standing, and walking. In addition to this, participants were able to join group exercise classes or receive another session of one-to-one therapy, if available. All three rehabilitation units were similar. Participants received multi disciplinary care from occupational therapists, speech pathologists and nurses.

Outcome measures

Blinded assessors assessed all participants before randomisation and at the end of the 4-week intervention period. Participants were asked not to discuss their training or group allocation with the assessors. The success of blinding was verified at the end of each participant's assessment by asking assessors to reveal whether they had become un-blinded. All assessors received training prior to assessment and were given assessment protocols to improve inter-rater reliability. Where possible, the same assessor was used to perform the initial and final assessments. Additional demographic data to describe the sample were collected prior to randomisation. These included Modified Rankin Scores, age, gender, time since injury, type of acquired brain injury, and affected side.

The primary outcomes were mobility and strength of the knee extensors of the affected lower limb. The secondary outcomes were strength of key muscles of the affected lower limb, strength of the knee extensors of the unaffected lower limb, and spasticity of the affected plantar flexors.

Mobility

Mobility was assessed using three items of the Functional Independence Measure: bed-chair transfer, walking and stairs. These three items were used to reflect participants' ability to walk and move around. Each item was rated on a 7-point scale based on level of assistance required to complete the task, with a score of 1 denoting total assistance and a score of 7 denoting complete independence. Scores for the three items were tallied for a total possible score of 21 points. Prior to the commencement of the study a mean between-group difference of 3 points was deemed clinically important for this outcome because an added benefit of 3 points could potentially alter the discharge destination for patients who require full assistance for transfers and walking.

Strength of the knee extensors of the affected lower limb

Maximal force was measured in Nm with a hand-held dynamometer. Each participant sat in his/her wheelchair or standardised armchair with feet clear off the floor facing a wall. A wooden wedge was placed under the thigh and the knee was placed in 90 deg flexion. The assessor identified the knee joint line and marked it with a pen. A line was drawn from just above the medial malleolus to just above the lateral malleolus on the affected lower limb. The distance from the knee joint line to the middle of the line around the ankle was measured. The pad of the dynamometer was placed perpendicular to the limb directly on top of the horizontal ankle line with the assessor's elbow firmly against the wall and wrist in a neutral position. The assessor did not push, but acted as a 'wall' for the participant to push against. Participants were given six maximal attempts with a 1-minute rest between each attempt. Each maximal attempt lasted 3 to 4 seconds and began with the assessor saying 'ready, steady, push'. The assessor provided the participant with strong verbal encouragement. The highest of the six maximal attempts was used as the measurement of strength. Torque was then calculated by multiplying force by the distance between the knee and point of application of the dynamometer. This method of measuring strength was tested prior to commencement of the study on 12 patients who were similar to those recruited to the study, and showed good inter-rater reliability with an intra-class correlation coefficient (3,1) of 0.91 (95% CI 0.62 to 0.98). Furthermore, hand-held dynamometry has been shown to have very good inter-rater reliability in rehabilitation patients,[17] as well as very good intra-rater reliability for measurements of strength in patients with neurological conditions.[18] Prior to the commencement of the study, a mean between-group difference equivalent to 20% of mean baseline strength was deemed clinically important for this outcome.

Strength of key muscles of the affected lower limb

The strength of the knee flexors and extensors, ankle dorsiflexors and plantar flexors were assessed using manual muscle testing.[19] Scores for the four muscle groups were combined and treated as a composite measure of lower limb strength, with 20 points representing the maximum score.

Strength of the knee extensors of the unaffected lower limb

The strength of the knee extensors of the unaffected lower limb was measured in Nm with a hand-held dynamometer using the same method as described for the affected lower limb.

Spasticity of the ankle plantar flexors of the affected lower limb

Spasticity of the ankle plantar flexors of the affected lower limb was assessed using the quality of the muscle reaction item of the Tardieu Scale where 0 indicates 'no resistance' and 4 indicates 'unfatigable clonus'.[20]

Data analysis

The sample size was calculated a priori. It was based on an 80% probability of detecting a mean between-group difference equivalent to 20% of mean initial strength. For the purposes of the power calculation, we needed to estimate the likely mean initial strength in raw units but on the understanding that this value would be adjusted post hoc. Mean initial strength was estimated to be 50 Nm,[21] with 20% equivalent to 10 Nm. The power calculation assumed a dropout rate of 5%, power of 80%, a significance level of 0.05, and a strong correlation (0.8) between initial and final values. It was based on an estimated SD of 18 Nm. The SD was derived from data collected prior to the study from 12 patients similar to those recruited to the study.

Data were analysed with a factorial analysis of covariance (baseline data) using a linear regression approach. The purpose of this analysis was to determine the effect of FES cycling versus no FES cycling on outcomes. All data were analysed according to the

Table 1
Baseline characteristics of participants.

Characteristic	Exp (n = 20)	Con (n = 20)
Age *(yr)*, mean (SD)	62 (15)	60 (16)
Gender, n male (%)	14 (70)	13 (65)
Time since ABI (*d*), median (IQR)	34 (22 to 49)	38 (24 to 72)
Type of ABI, n		
haemorrhage	4	5
infarct	13	9
traumatic brain injury	2	5
arteriovenous malformation	1	0
tumour	0	0
cerebral abscess	0	1
Affected side, n right (%)	11 (55)	12 (60)
Modified Rankin Scale (*points*), mean (SD)	4.5 (0.6)	4.5 (0.5)

ABI = acquired brain injury, Con = control group, Exp = experimental group.

principle of 'intention to treat'. The results for the primary analyses were interpreted with respect to the pre-defined minimum clinically worthwhile treatment effects. Minimum clinically worthwhile treatment effects were not set for the secondary outcomes, so these results were only interpreted with respect to statistical significance ($p < 0.05$).

Results

Flow of participants through the study

A total of 341 patients with acquired brain injury were screened over the trial period. Forty patients were randomised. The flow of the participants through the study is illustrated in Figure 1. Table 1 outlines the participants' demographics and baseline characteristics. The experimental and control groups were similar at baseline. On admission to the study most participants could not walk or needed a high level of assistance to walk/transfer. Only two participants were able to walk without assistance: they either had a score of ≤ 3 on the Modified Rankin Scale or ≥ 5 on the Functional Independence Measure. These scores reflect the severity of participants' disability. The mean composite score for the affected lower limb strength was 7 (SD 5) out of 20 points, reflecting severe weakness.

Adherence to the study protocol

Adherence to the intervention was good. Experimental participants received a median of 486 minutes (IQR 462 to 526) of FES cycling over a median of 20 sessions (IQR 19 to 20). This equated to a median of 25 minutes per session (IQR 24 to 25). Three participants deviated from the protocol. One participant in the experimental group became temporarily unwell and was transferred to an acute ward for some time during the intervention period. A second participant in the experimental group fell (not during a physiotherapy session) and sustained a fractured neck of femur, which required a total hip replacement; he was unable to continue the FES cycling. Both of these participants participated in the 4-week follow-up assessment. In addition, one participant in the experimental group died after randomisation; data were not imputed for this participant. Therefore 39/40 participants were included in the final analysis. The assessors remained blinded for all but one assessment.

Effect of FES cycling

The mean between-group difference for mobility was –0.3/21 points (95% CI –3.2 to 2.7). The upper bound of the 95% CI associated with the mean between-group difference for this outcome was less than the minimum worthwhile treatment effect of 3 points, indicating that the treatment was ineffective. The mean between-group difference for strength of the knee extensors of the affected lower limb was 7.5 Nm (95% CI –5.1 to 20.2). The 95% CI associated with the mean between-group difference for this outcome spanned the minimum worthwhile treatment effect (namely, 20% of mean initial strength, which was equivalent to 5.8 Nm), failing to rule in or rule out a clinically worthwhile treatment effect. The results for the secondary outcomes are in Table 2. Individual participant data are presented in Table 3 (see eAddenda for Table 3). There were no statistically significant between-group differences for spasticity of the plantar flexors of the affected lower limb or strength of the knee extensors of the unaffected lower limb. In contrast, there was a statistically significant between-group difference for the strength of key muscles of the affected lower limb, with a mean between-group difference of 3.0/20 points (95% CI 1.3 to 4.8).

Discussion

The results of this study indicate that 4 weeks of FES cycling in addition to usual care does not improve mobility in people with a sub-acute acquired brain injury (Table 2). These results are conclusive and cannot be explained by an insufficient sample size. The effects of FES cycling on strength of the knee extensors of the affected lower limb are unclear, with the results failing to determine whether or not there is a clinically worthwhile treatment effect. Unlike the results for mobility, these results may reflect an insufficient sample size.

Table 2
Mean (SD) of groups, mean (SD) difference within groups, and mean (95% CI) difference between groups. A positive mean between-group difference favours the experimental group for all outcomes except spasticity.

Outcome	Groups				Difference within groups		Difference between groups
	Week 0		Week 4		Week 4 minus Week 0		Week 4 minus Week 0
	Exp (n = 20)	Con (n = 20)	Exp (n = 19)	Con (n = 20)	Exp (n = 19)	Con (n = 20)	Exp minus Con
Mobility *(points/21)*	5.5 (3.8)	6.2 (4.5)	10.4 (6.5)	11.4 (7.4)	4.8 (4.2)	5.2 (5.0)	–0.3 (–3.2 to 2.7)
Strength of the knee extensors of the affected lower limb *(Nm)*	28.4 (27.0)	29.9 (26.2)	43.1 (29.2)	36.8 (32.0)	14.6 (23.0)	6.9 (15.2)	7.5 (–5.1 to 20.2)
Strength of key muscles of the affected lower limb *(points/20)*	6.5 (4.4)	7.6 (5.3)	10.5 (5.4)	8.5 (5.0)	4.1 (3.3)	1.0 (2.0)	3.0 (1.3 to 4.8)
Strength of the knee extensors of the unaffected lower limb *(Nm)*	63.9 (27.6)	58.7 (28.8)	70.9 (30.4)	64.7 (23.7)	5.5 (20.4)	6.0 (11.8)	0.9 (–9.4 to 11.2)
Spasticity of the ankle plantar flexors of the affected lower limb *(points/5)* [a]	1.8 (1.4)	0.9 (1.1)	2.1 (1.4)	1.3 (1.0)	0.2 (1.0)	0.4 (1.3)	0.3 (–0.5 to 1.0)

[a] A positive mean between-group difference favours the control group.
Con = control group, Exp = experimental group, Nm = Newton meters.
Small anomalies in subtraction are due to the effect of rounding.

Our failure to demonstrate a treatment effect on mobility contrasts with the results of the most relevant trial on FES cycling;[12] that trial demonstrated a treatment effect on walking. This is surprising because our training was more intensive (a median of 25 minutes five times a week for 4 weeks). It is possible that the difference in results may be due to the way we measured mobility. We did not solely focus on walking but instead used a composite Functional Independence Measure score that captured walking, transferring and negotiating stairs. Alternatively, perhaps there was an important difference between our participants and those of the previous trial. Many of our participants were cognitively impaired; this may have limited their ability to fully cooperate and to synchronise their lower limb movements in time with the FES cycle. We did not exclude those with poor cognition because we were interested in generalising our results to the typical population seen in the clinical setting. Perhaps future trials should consider using EMG-triggered FES cycling to help ensure that participants maximally contract their muscles in synchronisation with the cycle. However, the FES cycle used in this study did not provide this option.

We failed to determine whether or not FES cycling has clinically important effects on knee extensor strength of the affected lower limb (a primary outcome). This is most likely due to an insufficient sample size. Interestingly, we found a statistically significant between-group difference on our secondary outcome of strength of key muscles of the affected lower limb, with a mean between-group difference of 3.0/20 points (95% CI 1.3 to 4.8). Ambrosini et al also reported a statistically significant between-group difference on strength of key muscles of the affected lower limb in a study similar to ours, with a mean between-group difference of 19 points (95% CI 8 to 30) on a 100-point scale.[11] The results of their study are comparable to ours. Both sets of results are difficult to interpret without reference to a minimum clinically worthwhile treatment effect. If clinicians consider an added benefit of 1 point on a 20-point scale or 8 points on a 100-point scale as clinically worthwhile, then both sets of results would indicate that FES cycling has a clinically important effect on overall strength in the affected lower limb. However, presumably most clinicians and patients would want to see a larger added benefit than just 1 point (on a 20-point scale) or 8 points (on a 100-point scale) to justify the time, cost and effort of FES cycling. If this is the case, then our results and those of Ambrosini et al do not give a clear answer, despite the statistically significant between-group differences. To clarify this issue, a much larger study is required. However, any possible therapeutic effects of FES cycling on strength are of limited value unless accompanied by improvements in mobility.

Perhaps larger dosages of FES cycling are required to see changes in strength and mobility. That is, perhaps 60 minutes of FES cycling daily over 6 months with much higher (mA) intensities or increased resistance are required. However, it would be difficult to provide a higher dosage of FES cycling than provided in our study, given the constraints on healthcare systems. For example, few patients remain in hospital for 6 months following acquired brain injury, so FES cycling would have to be provided on an outpatient basis, which is logistically difficult. It is also unlikely that patients would tolerate more than 30 minutes a day of FES or FES administered at higher intensities or resistance.

A limitation of our study was that the initial strength of participants was highly variable. For example, composite strength in the affected lower limb ranged from 0/20 to 17/20 points. We included all participants that could potentially benefit from FES cycling in the clinical setting. In addition, participants who were both very weak and very disabled were also included. For example, the mean composite score for the affected lower limb strength was just 7/20 points (SD 5) and only two participants were able to walk without assistance. If those who are weaker and more disabled benefit more than those who are stronger and less disabled, then our inclusion of people with such a diverse range of strength and disabilities may have diluted a possible treatment effect. It is also possible that FES cycling has therapeutic effects on other variables not captured in our study, such as cardiovascular fitness.

The results of our trial are difficult to reconcile with the results of a recent systematic review on ES administered in various ways (excluding in conjunction with active cycling).[9] This review showed a small-to-moderate immediate treatment effect on strength (11 trials) and function (six trials) of ES versus no intervention. However, the results of this review need to be interpreted with caution because the median PEDro score for the trials included in the strength and functional analyses were 5 (IQR 4 to 6) and 6 (IQR 5 to 7) points with six (of 11 trials) and two (of six trials) failing to blind assessors, respectively. This indicates high susceptibility to bias, which may have inflated treatment effects. In contrast, we paid considerable attention to minimising all sources of bias. Our results, in combination with the results of this recent systematic review, make it difficult to recommend FES cycling to clinicians.

In summary, we found that 4 weeks of FES cycling in addition to usual care does not improve mobility in people with a sub-acute acquired brain injury. Future studies could clarify the effects of FES cycling on strength, although the clinical significance may be limited without accompanying effects on mobility.

What is already known on this topic: People with difficulty walking or moving around after acquired brain injury improve with intensive repetitive practice. Functional electrical stimulation cycling may assist further by stimulating muscle contractions in synchrony with the pedalling motion of a lower limb ergometer.

What this study adds: Functional electrical stimulation cycling does not improve mobility in people with acquired brain injury. The effects of functional electrical stimulation cycling on strength are unclear.

Footnotes: [a]Microsoft Excel, Microsoft, Redmond, USA; [b]RT300 cycle, Restorative Therapies, Baltimore, USA.

eAddenda: Table 3 can be found online at doi:10.1016/j.jphys.2016.08.004.

Ethics approval: Northern Sydney Local Health District Human Research Ethics Committee, South Eastern Sydney Local Health District Human Research Ethics Committee, Royal Rehab and The University of Sydney. Written consent was obtained from all participants or their next of kin before data collection began.

Competing interest: The authors declare no conflict of interest. The FES cycle used in this study was on loan from Restorative Therapies. The authors have no affiliation to Restorative Therapies and did not receive financial support from the company.

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Correspondence: Lisa Harvey, John Walsh Centre for Rehabilitation Research, Kolling Institute, Northern Sydney Local Health District, Sydney, Australia. Email: lisa.harvey@sydney.edu.au

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Chapter 5 Two weeks of intensive sit-to-stand training in addition to usual care improves sit-to-stand in people who are unable to stand up independently after stroke: a randomised trial

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Published manuscript

This project is presented as a published manuscript:

de Sousa DG, Harvey LA, Dorsch S, Varettas B, Jamieson S, Murphy A, Giaccari S. Two weeks of intensive sit-to-stand training in addition to usual care improves sit-to-stand ability in people who are unable to stand up independently after stroke: a randomised trial. Journal of Physiotherapy. 2019;65(3):152-158.

Conference proceedings

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

1. **de Sousa DG**, Harvey LA, Dorsch S, Jamieson S, Murphy A, Varettas B, Giaccari S. Strategies to increase amount and intensity of repetitive sit-to-stand training after stroke: insights from the REPS trial. World Confederation for Physical Therapy, Geneva, Switzerland, 2019.

2. **de Sousa DG**, Harvey LA, Dorsch S, Jamieson S, Murphy A, Varettas B, Giaccari S. Strategies to increase amount and intensity of repetitive sit-to-stand training after stroke: the REPS trial. Smart Strokes, Hunter Valley, Australia, 2019.

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Statement from co-authors confirming the authorship contribution of the PhD candidate. As co-authors of the manuscript:

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We confirm that Davide de Sousa has made the following contributions:

- Conception and design of the research including literature search
- Collection of data
- Analysis and interpretation of the findings
- Writing the manuscript, critical appraisal of content and response to reviewers

Name	Signature	Date
Lisa Anne Harvey		30-Aug-2019
Simone Dorsch		30-Aug-2019
Bronwyn Varettas		30-Aug-2019
Serena Jamieson		30-Aug-2019
Abby Murphy		30-Aug-2019
Sarah Giaccari		30-Aug-2019

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Research

Two weeks of intensive sit-to-stand training in addition to usual care improves sit-to-stand ability in people who are unable to stand up independently after stroke: a randomised trial

Davide G de Sousa [a,b], Lisa A Harvey [b], Simone Dorsch [c,d], Bronwyn Varettas [e], Serena Jamieson [e], Abby Murphy [e], Sarah Giaccari [e]

[a] Graythwaite Rehabilitation Centre, Ryde Hospital, Northern Sydney Local Health District; [b] John Walsh Centre for Rehabilitation Research, Kolling Institute, Sydney Medical School Northern, University of Sydney; [c] Faculty of Health Sciences, Australian Catholic University; [d] StrokeEd Collaboration; [e] Physiotherapy Department, Royal North Shore Hospital, Northern Sydney Local Health District, Sydney, Australia

KEY WORDS

Stroke
Sit-to-stand
Repetitive training
Physical therapy
Randomised trial

ABSTRACT

Question: Does intensive sit-to-stand training in addition to usual care improve sit-to-stand ability in people who are unable to stand up independently after stroke? **Design**: A multi-centre randomised controlled trial with concealed allocation, assessor blinding and intention-to-treat analysis. **Participants**: Thirty patients from two Sydney hospitals, < 3 months after stroke, with a mean Modified Rankin Scale score of 4 points (SD 0.5). **Intervention**: All participants received usual care. Participants in the experimental group attended two additional sessions of physiotherapy per day for 2 weeks. These sessions were individualised to the needs of each participant in order to increase the amount and intensity of sit-to-stand training. **Outcome measures**: Outcome measures were taken at baseline and at 2 weeks. The primary outcome was clinicians' impressions of sit-to-stand change, measured using videos and a 15-point Global Impressions of Change Scale. Secondary outcomes were sit-to-stand ability, composite strength of key muscles of the affected lower limb, gross lower limb extension strength, the Goal Attainment Scale, and ranking of change in ability to move from sitting to standing. **Results**: All participants completed the trial. The mean between-group difference for clinicians' impressions of sit-to-stand change was 1.57/15 points (95% CI 0.02 to 3.11). The secondary outcomes that indicated a treatment effect were gross lower limb extension strength and ranking of change in ability to move from sitting to standing, with mean between-group differences of 6.2 deg (95% CI 0.5 to 11.8) and −7 (95% CI −1 to −13), respectively. **Conclusion**: Two weeks of intensive sit-to-stand training in addition to usual care improves sit-to-stand ability in people who are unable to stand up independently after stroke. **Trial registration**: ANZCTR 12616001288415. **[de Sousa DG, Harvey LA, Dorsch S, Varettas B, Jamieson S, Murphy A, Giaccari S (2019) Two weeks of intensive sit-to-stand training in addition to usual care improves sit-to-stand ability in people who are unable to stand up independently after stroke: a randomised trial. *Journal of Physiotherapy* 65:152–158]**

Introduction

After stroke, many people have difficulty standing up and walking independently, due to motor impairments such as weakness and poor co-ordination. Loss of the ability to stand up can result in profound disability[1] and increased burden of care.[2] There is strong evidence that repetitive training of sitting,[3] standing up,[4] standing,[5] and walking[5] after stroke improves these functional tasks. There is also evidence that large amounts (more than triple the usual amount) of additional training improves functional outcomes after stroke.[6] However, it cannot be assumed that the effects of additional training are the same for all tasks because individual tasks may require different amounts of training. For example, tasks involving the upper limb appear to require more training than tasks involving the lower limb.[7]

Since standing up independently is essential for reducing disability and burden of care, it is important to understand if additional repetitive sit-to-stand training improves the ability to stand up independently after stroke. Five clinical trials have investigated the effects of additional repetitive sit-to-stand training after stroke.[8–12] Three of the five trials are not relevant for people who are very disabled and unable to stand up independently because these trials only recruited people who could stand up without assistance.[9,10,12] Another trial recruited a mix of people who could and could not stand up independently, and only provided a very imprecise estimate of the treatment effect.[11] The only remaining relevant trial, which specifically recruited people who could not stand up independently, had methodological issues affecting the validity of the results and did not provide intensive sit-to-stand training to participants.[8] Overall, these five trials do not provide clear evidence

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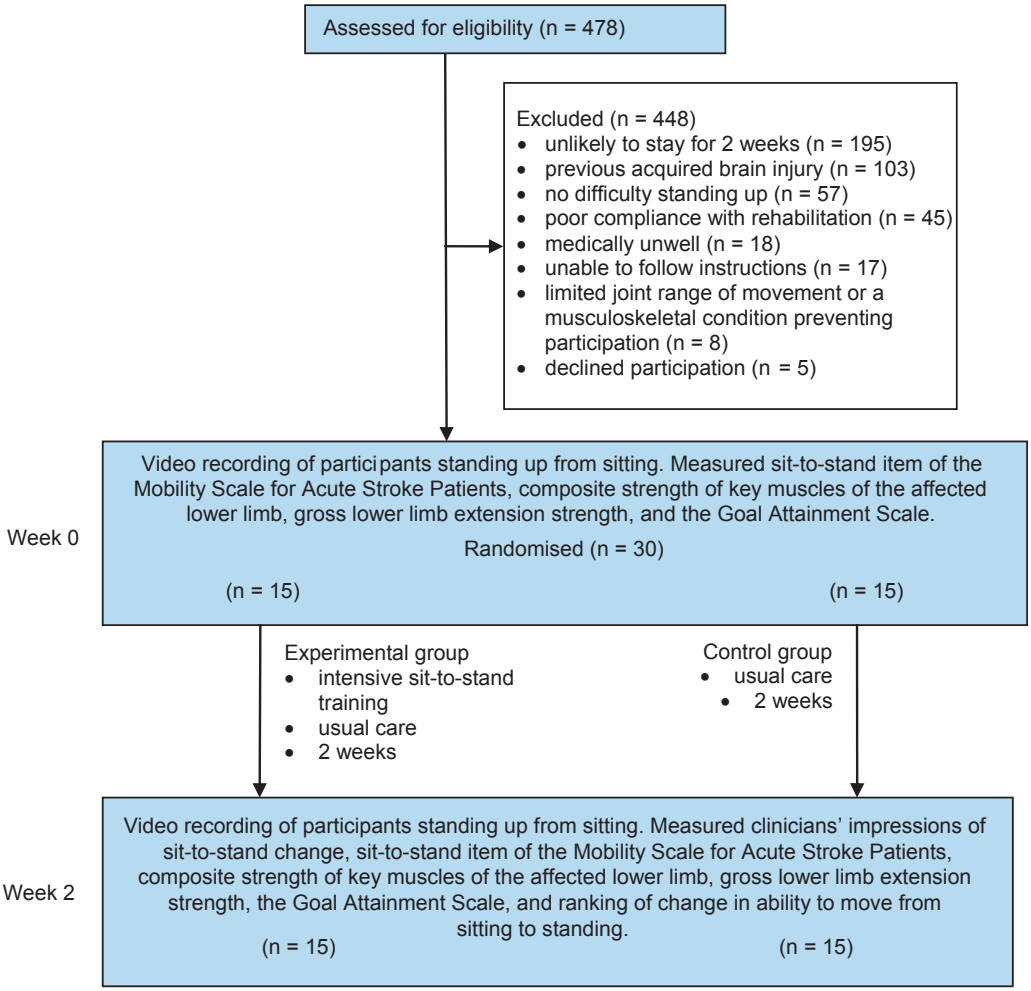

Figure 1. Design and flow of participants through the trial.

of the effectiveness of additional repetitive sit-to-stand training in people who are unable to stand up independently after stroke.

The primary aim of this trial was to determine if intensive sit-to-stand training in addition to usual care improves sit-to-stand ability in people who are unable to stand up independently after stroke.

Therefore, the research question for this multi-centre randomised controlled trial was:

> Does intensive sit-to-stand training in addition to usual care improve sit-to-stand ability in people who are unable to stand up independently after stroke?

Methods

Design

An assessor-blinded randomised controlled trial was undertaken (Figure 1). A person not involved in the trial created a blocked random allocation schedule for 30 participants using Microsoft Excel. The blocking ensured equal numbers of participants in the experimental and control groups. Participants' allocations were placed in opaque, sequentially numbered and sealed envelopes that were held offsite by a person not involved in the trial. Once participants passed the screening process and completed the initial assessment, trial staff contacted the independent person who opened an envelope and revealed the group allocation. Participants were considered to have entered the trial at this point. Participants were re-assessed at the end of the 2-week intervention period. All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed.

Participants

All patients admitted to two hospitals between 21 June 2016 and 16 October 2018 were screened for inclusion. The inclusion criteria were as follows: first-time stroke or any other non-progressive acquired brain injury; $<$ 6 months after stroke or brain injury; difficulty standing up due to the effects of stroke or brain injury; and sufficient communication skills to indicate yes/no verbally or via gestures. Patients were excluded for any of the following reasons: limited passive joint range of movement or musculoskeletal conditions that would prevent participation; inability to participate in exercise (ie, medically unwell or unable to tolerate usual physiotherapy); and expected length of stay $<$ 2 weeks.

Experimental group

Participants allocated to the experimental group participated in two additional sessions of physiotherapy per day for 2 weeks in addition to usual care. Each additional session was at least 30 minutes during the week (hence, an additional 1 hour per day) and 1 hour on the weekend (2 hours per day). However, the sessions were sometimes longer than this if tolerated by the participants. The sessions were individualised to the needs of each participant in order to increase the amount and intensity of sit-to-stand training (see Box 1). All sit-to-stand training was based on the principles of task-specific motor training, with an emphasis on repetition, and the use of visual targets to provide an external focus to the movement. Training also incorporated verbal feedback. Intensity of training was increased by increasing the number of repetitions performed in a specified time. Training was also steadily progressed by lowering the

Box 1. Protocol and progression of sit-to-stand training.

Participants who could perform the whole sit-to-stand task from raised treatment beds with supervision were set up with a wall on their unaffected side and chairs or tables around them so they could practise moving from sitting to standing repetitively and safely.

If participants were unable to perform the whole sit-to-stand task, they performed part-practice of components of the sit-to-stand task until they were able to move from sitting to standing with assistance. For example, if participants could not move from sitting to standing due to weakness and poor co-ordination of their affected lower limb extensors, they performed many repetitions of squats on a sliding tilt-table.

If participants could not move from sitting to standing due to weakness and poor co-ordination of their affected lower limb hip flexors and extensors, they performed many repetitions of reaching beyond their arms' length for targets whilst loading their affected lower limb.

Participants were encouraged to achieve a daily target of sit-to-stand repetitions. If they could not reach this target, they were encouraged to perform as many repetitions of the sit-to-stand task per day as they could tolerate.

Participants were provided with visual targets (ie, tape on a wall to provide a visual target for shoulder alignment, or tape on a chair corresponding with tape on the knee of their affected lower limb to provide a target for knee alignment prior to moving from sitting to standing).

Verbal feedback about the quality of participants' movements were also provided.

Intensity of training was increased by increasing the amount of repetitions performed in a specified time.

Progression of sit-to-stand training followed these general principles:
Training was made progressively more difficult to continue to challenge each participant's motor ability.

If participants could achieve more than 50 repetitions in $<$ 15 minutes, the exercise was made more difficult.

If participants were unable to achieve 25 repetitions within 15 minutes, the exercise was made easier.

The new version of the exercise was adopted until more than 100 repetitions were achieved following the method above.

If participants could not perform a previously tolerated exercise on a specific day for any reason (ie, they were medically unwell) but were stable enough to participate in therapy, the task was made easier so that the day's repetition target could be achieved.

Training was also steadily progressed by lowering the height of treatment beds, altering foot position to increase weight-bearing through the affected lower limb, and standing up with a foam mat under the feet. All these strategies were used to ensure that each participant trained at his/her maximal capacity.

height of treatment beds, altering foot position to increase weight-bearing through the affected lower limb, and standing up with a foam mat under the feet. All these strategies were used to ensure that each participant trained at his/her maximal capacity. Additional strategies were used to facilitate extra sit-to-stand training during therapy hours and after hours (Table 1). Both the experimental and control groups received usual care, namely two 1-hour sessions of physiotherapy each weekday.

One therapist with over 10 years of experience in neurological physiotherapy was responsible for treating all experimental participants and did not treat any of the control participants. Attempts were made to keep the therapists responsible for treating the control participants naïve to the purpose of the trial. That is: they were not told the purpose of the trial or the details of the intervention. Similarly, all participants were kept naïve to the purpose of the trial. For example, the participant information sheets and consent forms did not disclose the specific experimental intervention, and experimental participants were not told that they were specifically focusing on sit-to-stand.

Control group

Participants allocated to the control group received usual care only. A detailed description of usual care is presented in the next section.

Table 1
Strategies individualised to the needs of each participant to increase the amount of sit-to-stand training.

Strategies	Exp	Con
Physiotherapy gym $\geq$ 3 hours/weekday	Provided	Not provided
Semi-supervised practice	Provided	Ad hoc
Therapy on weekend days	Provided	Not provided
Exercise diary	Provided	Not provided
Structured training for carers/family	Provided	Ad hoc and unstructured
Individualised after-hours exercise program	Provided	Ad hoc

Con = control group, Exp = experimental group.

Usual care

Usual care consisted of two 1-hour sessions of physiotherapy each weekday. This therapy involved strength, endurance, balance and co-ordination exercises as well as task-specific training of sitting, sit-to-stand, standing, and walking. Exercise repetitions for both groups were counted using a hand-held counter. The time that participants participated in therapy was recorded. The two hospitals were similar and participants received multi-disciplinary care from occupational therapists, speech pathologists and nurses.

Outcome measures

All participants were assessed by a blinded assessor before randomisation and at the end of the 2-week intervention period. Participants were asked not to discuss their training or group allocation with the assessors. The success of blinding was verified at the end of each participant's assessment by asking assessors to reveal whether they had become un-blinded. All assessors received training prior to commencement of the trial and were given assessment protocols to improve inter-rater reliability. Where possible, the same assessor was used to perform the initial and final assessments. Additional demographic data to describe the sample were collected prior to randomisation. This included Modified Rankin Scale scores, age, gender, time since injury, type of acquired brain injury, and affected side.

The primary outcome was clinicians' impressions of sit-to-stand change. The secondary outcomes were sit-to-stand ability using the sit-to-stand item of the Mobility Scale for Acute Stroke Patients, composite strength of key muscles of the affected lower limb, gross lower limb extension strength, the Goal Attainment Scale, and ranking of change in ability to move from sitting to standing.

Clinicians' impressions of sit-to-stand change

Change in sit-to-stand ability was assessed using a 15-point Global Impressions of Change Scale.[13] This involved taking short video recordings of participants attempting or performing an independent sit-to-stand at baseline and again at 2 weeks. Each video was

between 2 and 5 minutes in duration and the angle of the camera and distance between the camera and participant were standardised. Participants were permitted to wear shoes but lower limb aids and orthoses were removed and standardised for both assessments. Participants were positioned in the middle of a treatment bed set at a height of 60 cm, with their ankles in dorsiflexion and their heels on the ground. Participants were asked to stand up with their arms crossed over their chests. If participants could not stand up independently, they were permitted to place their arm/s on their thigh/s to assist. If participants still could not stand up independently, they were permitted to push through their hands on the bed to assist with standing up. If participants still could not stand up independently, assistance was provided by a physiotherapist not involved in the trial and blinded to group allocation. If necessary, a second person provided assistance for participants to stand up. If participants could stand up independently from 60 cm, the bed height was incrementally lowered by 5 cm, and then a further 5 cm after every successful attempt at standing up. The assessment ceased when participants could no longer stand up independently, or could not stand up safely with maximal assistance of two people. If participants were initially unable to stand up with assistance of two people from a height of 60 cm, they were challenged to reach beyond their arms' length to the limits of their abilities whilst seated.

All videos were collated into pairs corresponding with the initial and final assessment of each participant. Thirty pairs of videos were generated (60 videos in total) and viewed on two separate adjoining screens. The video taken at the time of a participant's initial assessment always appeared on the left screen and the final assessment on the right. Two blinded assessors (one with $>$ 20 years and one with 4 years neurological physiotherapy experience) were asked to separately view the pairs of videos and rate the change in the ability of participants to move from sitting to standing independently, using a Global Impressions of Change Scale. Assessors were asked to take into consideration the severity of participants' disabilities and the amount of change expected over a 2-week period. The Global Impressions of Change Scale is a 15-point scale with -7 representing 'very much worse', 0 representing 'no difference', and $+7$ representing 'very much better'. A mean between-group difference of 2/15 points was considered clinically important for this outcome prior to the commencement of the trial.

Sit-to-stand ability

Sit-to-stand ability was also assessed using the sit-to-stand item of the Mobility Scale for Acute Stroke Patients.[14] This item is rated on a 6-point scale based on level of assistance required to move from sitting to standing. A score of 1 denotes inability to move from sitting to standing and a score of 6 denotes the ability to move from sitting to standing unassisted, safely, and with no verbal input.

Composite strength of key muscles of the affected lower limb

The strength of the hip extensors, knee extensors, and plantar flexors of the affected lower limb were assessed using the Manual Muscle Test, consisting of 6 grades (ie, 0 = no muscle contraction to 5 = moves joint through full available range and holds against maximal resistance).[15] Scores for the three muscle groups were combined and treated as a composite measure of lower limb extensor strength, with 15 points representing the maximum score.

Gross lower limb extension strength

Gross lower limb extension strength of the affected lower limb was assessed using an inclinometer on a sliding tilt table. Each participant was transferred to a sliding tilt table. The participant was positioned with the affected lower limb on the foot plate and the knee in 70 deg of flexion. The unaffected lower limb was not weight-bearing. The tilt table was raised and the participant was instructed to extend the affected lower limb. The highest degree of incline against which the participant could extend the affected lower limb was recorded, where zero degrees indicated that the tilt table was horizontal and 90 degrees indicated that the tilt table was vertical.

Table 2
Baseline characteristics of participants.

Characteristic	Exp (n = 15)	Con (n = 15)
Age *(yr)*, mean (SD)	62 (17)	69 (16)
Gender, n male (%)	9 (60)	8 (53)
Time since ABI *(d)*, median (IQR)	16 (13 to 57)	18 (10 to 34)
Type of ABI, n		
haemorrhage	5	1
infarct	10	14
Affected side, n right (%)	5 (33)	6 (40)
Modified Rankin Scale *(points/7)*, mean (SD)	4.2 (0.4)	4.1 (0.6)

ABI = acquired brain injury, Con = control group, Exp = experimental group.

The Goal Attainment Scale

The original intention was to ask participants to identify one personal goal related to their sit-to-stand ability. However, preliminary testing of this scale indicated that patients with cognitive or verbal impairments had great difficulty setting specific goals. Therefore, the Goal Attainment Scale was modified prior to beginning the trial.[16] Prior to randomisation, a blinded assessor set one goal related to sit-to-stand ability, which was based on their predictions of expected gains in participants' ability to move from sitting to standing over the 2-week intervention period. The assessor who set the initial goal considered the severity of the participant's disabilities and the expected ability of the participant to tolerate therapy. The goal was set according to the SMART principle, that is: the goal was specific, measurable, attainable, realistic and timely. A blinded assessor rated attainment of the goal at the 2-week assessment. The goal was rated on a 5-point scale, where '0' denoted the expected level of achievement; '+1' and '+2' were respectively 'a little' and 'a lot' better than expected, whilst '−1' and '−2' were correspondingly 'a little' and 'a lot' less than expected. A higher score reflected better achievement of goals than a lower score.

Ranking of change in ability to move from sitting to standing

Two blinded assessors separately ranked the change in the participants' abilities to move from sitting to standing in order from most improved to least improved. The assessors used the videos collected as part of the primary outcome to determine each participant's ranking. Scores were combined and averaged to minimise the impact of extreme scores.

Data analysis

The sample size was calculated a priori. It was based on an 80% probability of detecting a mean between-group difference of 2/15 on the primary outcome: clinicians' impressions of sit-to-stand change. The power calculation assumed a drop-out rate of 15%, a power of 80%, an alpha of 0.05, and a strong correlation (0.8) between initial and final values. It was based on an estimated SD of 1.5 derived from a previous study.[17]

Each outcome was analysed using a linear regression approach with baseline data as a covariate. The purpose of these analyses was to determine the effect of the intensive sit-to-stand training versus usual care on all outcomes. All data were analysed according to the principle of 'intention to treat'. The result for the primary analysis was analysed with respect to the pre-defined minimum worthwhile treatment effects. Minimum worthwhile treatment effects were not set for the secondary outcomes.

Results

Flow of participants through the trial

A total of 478 patients with acquired brain injury were screened from the two hospitals over the trial period. Thirty patients were randomised. The flow of the participants through the trial is illustrated in Figure 1. Table 2 summarises the demographic and clinical characteristics of the participants at baseline. The

Table 3
Mean (SD) of groups, mean (SD) difference within groups, and mean (95% CI) difference between groups.

Outcome	Groups				Difference within groups		Difference between groups
	Week 0		Week 2		Week 2 minus Week 0		Week 2 minus Week 0
	Exp (n = 15)	Con (n = 15)	Exp (n = 15)	Con (n = 15)	Exp	Con	Exp minus Con
Clinicians' impressions of sit-to-stand change *(points/15)*			4.9 (1.6)	3.3 (2.5)			1.57 (0.02 to 3.11)
Sit-to-stand ability *(points/6)*	2.2 (1.1)	3.2 (1.5)	3.9 (1.7)	4.3 (1.9)	1.7 (1.3)	1.1 (0.7)	0.6 (−0.2 to 1.5)
Composite strength of key muscles of the affected lower limb *(points/15)*	6.9 (3.5)	7.1 (3.0)	8.0 (4.2)	8.1 (3.2)	1.1 (2.2)	1.1 (1.6)	0.1 (−1.4 to 1.5)
Gross lower limb extension strength *(deg)*	21.3 (14.9)	21.7 (10.6)	30.5 (15.3)	24.7 (12.8)	9.2 (7.5)	3.0 (7.5)	6.2 (0.5 to 11.8)
Goal Attainment Scale *(points/5)*			0.7 (1.4)	−0.1 (1.1)			0.7 (−0.2 to 1.7)
Ranking of change in ability to move from sitting to standing[a]			12 (8)	19 (8)			−7 (−1 to −13)

Shaded row = primary outcome. Small anomalies in subtraction are due to the effects of rounding. A positive between-group difference favours the experimental group, except where indicated.
Con = control group, Exp = experimental group.
[a] A negative between-group difference favours the experimental group.

experimental and control groups were similar at baseline. Most participants could not walk or needed a high level of assistance to transfer or walk on admission to the trial.

Adherence to the trial protocol

Adherence to the intervention was good. Experimental participants participated in a median (IQR) of 1920 minutes (1690 to 2273) of physiotherapy over the 2-week intervention period. This equated to a median (IQR) of 137 minutes (121 to 162) per day. Control participants participated in a median (IQR) of 970 minutes (948 to 1088) of physiotherapy over the 2-week intervention period. This equated to a median (IQR) of 97 minutes (95 to 109) per day.

Experimental participants completed a median (IQR) 1252 sit-to-stand repetitions (763 to 1773) over the 2-week intervention period. This equated to a median (IQR) 89 sit-to-stand repetitions (55 to 127) per day. Control participants completed a median (IQR) 365 sit-to-stand repetitions (164 to 514) over the 2-week intervention period. This equated to a median (IQR) 37 sit-to-stand repetitions (16 to 51) per day. The assessors remained blinded for all assessments. There were no adverse events.

Effect of sit-to-stand training

Primary outcome

The mean between-group difference for clinicians' impressions of sit-to-stand change was 1.57/15 points (95% CI 0.02 to 3.11) (Table 3). The upper end of the 95% CI associated with the mean between-group difference for this outcome exceeded the minimum worthwhile treatment effect of 2 points, indicating uncertainty as to whether the treatment effect was clinically worthwhile. Individual participant data for this and the secondary outcomes are presented in Table 4 on the eAddenda.

Secondary outcomes

The results for the secondary outcomes are presented in Table 3. The mean between-group difference for sit-to-stand ability was 0.6/6 points (95% CI −0.2 to 1.5). The mean between-group difference for composite strength of the key muscles of the affected lower limb was 0.1/15 points (95% CI −1.4 to 1.5). The mean between-group difference for gross lower limb extension strength was 6.2 deg (95% CI 0.5 to 11.8). The mean between-group difference for the Goal Attainment Scale was 0.7/5 points (95% CI −0.2 to 1.7). The mean between-group difference (95% CI) for ranking of change in ability to move from sitting to standing was −7 (95% CI −1 to −13) in favour of the experimental group, supporting the results of the primary outcome.

Discussion

The results of this trial indicate that intensive sit-to-stand training in addition to usual care improves sit-to-stand ability in people who are unable to stand up independently after stroke (Table 3). This trial provides the first evidence that as little as 2 weeks of additional repetitive sit-to-stand training in the early stages of stroke recovery may be worthwhile.

There have been trials investigating the effects of additional repetitive sit-to-stand training; however, some of these trials only recruited people who could stand up without assistance.[9,10,12] Barreca et al specifically recruited people who could not stand up independently after stroke; however, this trial had methodological issues affecting the validity of the results.[8] Interestingly, Barreca et al demonstrated a treatment effect with a small difference in daily sit-to-stand repetitions between their experimental and control groups: median 15 repetitions (IQR 12 to 20) versus 11 repetitions (IQR 8 to 17), respectively. This improvement with such a small difference in daily sit-to-stand repetitions between groups conflicts with recent evidence[6] indicating that large amounts (more than triple the usual amount) of additional training are required to improve functional outcomes after stroke. In comparison, participants in the experimental and control groups in our trial performed a median of 89 (IQR 55 to 127) versus 37 (IQR 16 to 51) daily sit-to-stand repetitions, respectively. Overall, participants in our experimental group performed over three times more sit-to-stand repetitions than participants in our control group; median (IQR) 1252 repetitions (763 to 1773) versus 365 repetitions (164 to 514), respectively. It is unclear how Barreca et al demonstrated a treatment effect with such a small difference in sit-to-stand repetitions between their experimental and control groups. However, there are two possible explanations: they may have under-reported the total amount of sit-to-stand repetitions in their experimental group or it may be that less additional training is needed to improve sit-to-stand than other tasks (such as reaching and manipulation) in people after stroke. We developed our protocol on the hypothesis that large amounts of sit-to-stand repetitions are needed to improve sit-to-stand ability; however, we may have provided more training than is required. A further trial comparing different amounts of sit-to-stand repetitions is needed to further explore this issue.

While our trial demonstrated a treatment effect of additional sit-to-stand training, there is uncertainty as to whether the size of

this effect is clinically worthwhile. This is due to the imprecision of the estimate associated with the between-group difference. The upper end of the 95% CI exceeded the pre-determined clinically worthwhile treatment effect of 2/15 points. A larger sample size would have provided more precision and possibly more clarity around whether the treatment was worthwhile.

It is possible that a larger treatment effect would have been found if there had been better control of contamination between groups. Physiotherapists may have unintentionally incorporated some of the experimental strategies to improve sit-to-stand ability with participants in the control group. This potential contamination may have increased the amount of training provided to control participants, thereby decreasing the difference between the two groups. Prior to the start of the trial, we considered treating experimental participants in a separate area to avoid contamination. However, this was not feasible. To minimise contamination, the same physiotherapist provided all the interventions to participants in the experimental group and great care was taken to keep experimental participants naïve to the purpose of the trial. Whilst experimental participants were clearly participating in the additional training, they were unaware that the content was different to usual care. Similarly, attempts were made to keep the therapists responsible for treating the control participants naïve to the purpose of the trial. Despite the potential contamination, a treatment effect was still demonstrated.

We administered intensive sit-to-stand training over 2 weeks. We chose 2 weeks because people often only remain in rehabilitation for this period and we were interested to know whether it is worth administering intensive sit-to-stand training if it can only be provided for such a short length of time. The results indicate that this intervention is effective for people who only receive 2 weeks of rehabilitation after stroke. It may be that larger amounts of sit-to-stand training over a longer period would have produced even greater results. The other reason we administered the treatment for 2 weeks was that we were concerned that participants would not tolerate such an intensive intervention each day for more than 2 weeks, particularly in the early stages of stroke recovery. However, we found that the experimental participants were able to tolerate large amounts of sit-to-stand repetitions, suggesting that our concerns were unfounded.

One of the challenges prior to the start of this trial was finding an outcome measure that would be appropriate for people with all levels of disability and particularly those who were very disabled. Most outcome measures of sit-to-stand ability are susceptible to floor effects in people who are too disabled to stand up. To overcome this problem, we used a novel method to assess sit-to-stand ability: clinicians' impressions of change of participants' ability to move from sitting to standing from videos. Two blinded assessors were asked to score the change in ability of participants to perform an independent sit-to-stand movement, taking into consideration the initial disability of the participant and the amount of change expected over a 2-week period assuming the participant received usual care. This way, small functional changes that are often missed by other outcome measures could be detected. A limitation of this outcome measure is that it is somewhat subjective and relies on the clinicians' understanding of likely change in ability to move from sitting to standing over a 2-week period after taking into account the severity of participants' disabilities. We used two assessors and averaged their scores to minimise the impact of extreme scores. Interestingly, the results of one of the secondary outcomes, which also relied on the scores from videos, gave similar results. Taken together, the results of these two outcomes add weight to the potential value of relying on clinicians' impressions of change of participants' ability to move from sitting to standing from videos.

This trial provides insights into the possible mechanisms underlying the observed improvements in sit-to-stand ability. That is: repetitive practice of sitting to standing improves lower limb strength, which in turn improves sit-to-stand ability. Interestingly, there was no suggestion of a between-group difference for composite strength of key muscles of the affected lower limb. In contrast, the between-group difference for gross lower limb extension strength of the affected lower limb suggested a treatment effect (6.2 deg, 95% CI 0.5 to 11.8). These conflicting results of voluntary muscle strength may highlight the lack of sensitivity in the manual muscle test scale used to assess composite strength of key muscles of the affected lower limb. The improvements in gross lower limb extension strength of the affected lower limb suggest that the observed improvement in sit-to-stand ability may, in part, be explained by an improvement in lower limb extensor strength. This finding aligns with other studies of repetitive practice after stroke.[18]

We planned to use the Goal Attainment Scale to assess if participants could achieve personal goals related to sit-to-stand ability. However, preliminary testing of this scale indicated that patients with cognitive or verbal impairments had great difficulty setting specific goals. Therefore, we modified the goal-setting procedure for the Goal Attainment Scale prior to beginning the trial. Prior to randomisation, a blinded assessor set one goal related to sit-to-stand ability, which was based on his/her predictions of expected gains in participants' ability to move from sitting to standing over the 2-week intervention period. Similar to the primary outcome measure, the assessor who set the initial goal took into account the severity of the participants' disabilities and expected ability of participants to tolerate therapy. The results for the Goal Attainment Scale did not suggest a treatment effect; however, these findings may point to problems with the way the Goal Attainment Scale was used in this trial.

Some clinicians may view the inclusion of participants with varying levels of cognition, aphasia, and lower limb strength as a limitation. If those who are weaker and more disabled benefit more than those who are stronger and less disabled, then the inclusion of people who were less disabled may have reduced the treatment effect. However, we see this as a strength and not a limitation in our trial. Participation was not limited to a more disabled group of people because we were interested in generalising the results to typical patients admitted for rehabilitation after stroke. However, only participants who were unable to stand up independently were included in the trial.

The results of this trial are important because up until now there has been uncertainty regarding the effectiveness of additional repetitive sit-to-stand training in people who are unable to stand up independently after stroke. Since standing up independently is essential for reducing disability and burden of care, attaining independence in sit-to-stand ability is a high priority. However, there can be many tasks to train after stroke, and it can be difficult for clinicians to prioritise which tasks to train first. One possible implication of our results is that 2 weeks of intensive repetitive sit-to-stand training could be initially prioritised for people with difficulty standing up, allowing more time after this period to focus on other tasks requiring independent sit-to-stand ability, such as walking.

In summary, this trial provides evidence that as little as 2 weeks of intensive sit-to-stand training in addition to usual care improves sit-to-stand ability in people who are unable to stand up independently after stroke. This trial also demonstrates that large amounts of sit-to-stand training is well tolerated in the early stages of stroke recovery. Future larger trials should clarify the effects of longer training periods or different amounts of sit-to-stand repetitions, and determine if the observed effects are clinically worthwhile.

What was already known on this topic: After stroke, many people have difficulty standing up independently. Repetitive training improves functional tasks, but existing trials of repetitive sit-to-stand training have important limitations.

What this study adds: Two weeks of intensive sit-to-stand training in addition to usual care improves sit-to-stand ability in people who are unable to stand up independently after stroke. However, it is not clear whether the size of the treatment effect is clinically worthwhile. Large amounts of sit-to-stand training are well tolerated in the early stages of stroke recovery.

eAddenda: Table 4 can be found online at: https://doi.org/10.1016/j.jphys.2019.05.007.

Ethics Approval: The study was approved by the Northern Sydney Local Health District Human Research Ethics Committee. Written consent was obtained from all participants or their next of kin before data collection began.

Competing interests: Nil.

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Correspondence: Davide de Sousa, John Walsh Centre for Rehabilitation Research, Kolling Institute, Northern Sydney Local Health District, Sydney, Australia. Email: davidedesousa@gmail.com

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Chapter 6 Discussion

This chapter is divided into the following sections:

- The primary objectives and key findings of this research program.
- An overview of each study conducted in this research program including results, strengths, limitations and implications for future research.

This chapter will not include a detailed discussion of the results of this research program. Each publication contained in chapters 3 to 5 of this thesis contains separate discussion sections where study results are discussed in detail and compared to other research.

Primary objectives of the research program

The primary objectives of the research program were:

1. To determine if interventions involving repetitive practice improve strength after stroke, and if any improvements in strength are accompanied by improvements in activity.
2. To determine if four weeks of FES cycling in addition to usual care improves mobility and strength in people with a sub-acute acquired brain injury caused by stroke or trauma.
3. To determine if intensive sit-to-stand training in addition to usual care improves sit-to-stand ability and gross lower limb extension strength in people who are very weak and immobile after stroke.

Key findings of the research program

There were three key findings of the research program:

1. Interventions involving repetitive practice improve strength after stroke, and these improvements are accompanied by improvements in activity.

2. Functional electrical stimulation cycling does not improve mobility in people with acquired brain injury and its effects on strength are unclear.
3. Two weeks of intensive sit-to-stand training in addition to usual care improves sit-to-stand in people who are unable to stand up independently after stroke.

Overview of the research program

Study one: a systematic review

The aim of this systematic review was to determine if interventions involving repetitive practice improve strength after stroke, and if any improvements in strength are accompanied by improvements in activity.

Study one results

The results of the primary analysis on strength and the secondary analyses on upper and lower limb activity are presented below:

- Forty-six studies with a total of 1928 participants investigated the effects of repetitive practice on strength after stroke. The overall SMD of repetitive practice on strength when the upper and lower limb studies were combined was 0.25 SD (95% CI 0.16 to 0.34, $I^2 = 44\%$) in favour of repetitive practice (see Figure 3 in the publication for the detailed forest plot).
- Twenty-four studies with a total of 912 participants investigated the effects of repetitive practice on upper limb activity after stroke. The SMD was 0.15 SD (95% CI 0.02 to 0.29, $I^2 = 50\%$) in favour of repetitive practice on upper limb activity (see Figure 4 in the publication for the detailed forest plot).
- Twenty studies with a total of 952 participants investigated the effects of repetitive practice on lower limb activity after stroke. The SMD was 0.25 SD (95% CI 0.12 to 0.38, $I^2 = 36\%$) in favour of repetitive practice on lower limb activity (see Figure 5 in the publication for the detailed forest plot).

Strengths of study one

The following are strengths of study one:

- Study one was a large systematic review of 52 studies with meta-analysis. Systematic reviews are considered the highest level of research evidence.
- We followed the Cochrane methodology for conducting systematic reviews. Special attention was given to assessing the risk of bias in the included studies.
- The systematic review protocol was prospectively registered with PROSPERO.
- A thorough search strategy was developed and several databases were searched.
- The manuscript was peer-reviewed and published in the highest-ranked physiotherapy journal.
- SMD were back-converted to provide results in clinically relevant measures, such as Newton metres or percentage of improvement from baseline strength.
- This systematic review is the only review to specifically investigate the effect of repetitive practice on strength after stroke. All other reviews combined studies that investigated other forms of strengthening interventions with studies investigating the effects of repetitive practice.
- This systematic review is the only review to provide individual estimates of improvements in strength for 12 different types of interventions involving repetitive practice.

Limitations of study one

The following are limitations of study one:

- A minimal worthwhile treatment effect was not defined a priori making it difficult to determine if a statistically significant result was clinically worthwhile.
- A SMD was used instead of MD making it difficult for clinicians to interpret the results.
- Post data were used instead of change data (since post data were most commonly reported in studies). Change data may have improved precision around the point

estimate allowing for better conclusions to be made regarding the effectiveness of repetitive practice to improve strength.

- There were insufficient data from the included studies to perform subgroup analyses on dosage (repetitions of active practice) and initial strength (weak i.e. ≤ 3/5 MRC versus strong i.e. ≥ 4/5 MRC). Therefore, an arbitrary amount of time was used for the dosage comparison (≤ 24 hours versus > 24 hours of repetitive practice) and scheduled therapy time was primarily used over actual therapy time, since these data were reported more often. The subgroup analysis on initial strength could not be performed.

Implications for future research

This systematic review highlighted significant gaps and limitations in the research evidence for interventions involving repetitive practice. The following points highlight the implications for future research:

- Clinical trialists should make every effort to minimise bias in randomised controlled trials and should prospectively register trials on a clinical trial registry.
- Many of the included studies in the systematic review had 'unclear' methods of minimising bias due to poor reporting. Randomised controlled trials need to be reported according to the CONSORT guidelines.
- All outcome data (i.e. post, change, and participant-level data) should be reported in clinical trials to facilitate more precise analyses and thus better conclusions on clinical effectiveness.
- Future clinical trials of repetitive practice should report dosage as repetitions of active practice rather than scheduled time or actual time in therapy. Data on repetitions of active practice are more accurate for understanding the effects of individual interventions on strength and activity after stroke.

- Further large clinical trials are needed to understand the impact of initial strength or severity of stroke on outcomes. These data will inform clinical practice and may change approaches to prescription of repetitive practice, and even rehabilitation programs.

Study two: a randomised controlled trial

The aim of this randomised controlled trial was to determine if four weeks of active FES cycling in addition to usual care improves mobility and strength more than usual care alone in people with a sub-acute acquired brain injury caused by stroke or trauma.

Study two results

The results of the primary outcomes for mobility and strength of the knee extensors of the paretic lower limb, and secondary outcome for strength of key muscles of the paretic lower limb are presented below:

- The mean between-group differences (95% CI) for mobility and strength of the knee extensors of the paretic lower limb were -0.3/21 points (-3.2 to 2.7) and 7.5Nm (-5.1 to 20.2), respectively, where positive values favour the experimental group.
- The only secondary outcome that suggested a possible treatment effect was strength of key muscles of the paretic lower limb with a mean between-group difference (95% CI) of 3.0/20 points (1.3 to 4.8).

Strengths of study two

The following are strengths of study two:

- Study two was a high quality randomised controlled trial with careful attention given to minimising bias (8/10 points on the PEDro scale).
- The randomised controlled trial protocol was prospectively registered on Australian New Zealand Clinical Trials Registry.

- The manuscript was peer-reviewed and published in the highest-ranked physiotherapy journal.
- There was good adherence to the study protocol and participants received a median (IQR) of 25 minutes (24 to 25) of FES cycling per session.
- The study had broad inclusion criteria. Thus, the results can be generalised to typical patients admitted to sub-acute rehabilitation with acquired brain injury.
- The results clearly demonstrated that FES cycling does not improve mobility in people with acquired brain injury. These results are conclusive and cannot be explained by an insufficient sample size. That is, the upper bound of the 95% CI associated with the mean between-group difference failed to cross the minimally worthwhile treatment effect of 3 points.

Limitations of study two

The following are limitations of study two:

- The sample size may have been insufficient to determine the effects of FES cycling on strength of the knee extensors of the paretic lower limb. This was due to the wide 95% CI associated with the mean between-group difference spanning the minimally worthwhile treatment effect for this outcome.
- Participants in the study had a wide range of impairments (i.e. aphasia, poor cognition, varied levels of strength) which may have prevented them from fully cooperating with the intervention. Functional Electrical Stimulation is typically used on muscles that cannot generate sufficient force to move limbs against gravity. There may be differences in the way people with very weak muscles respond to FES cycling versus people with stronger muscles.

Implications for future research

This randomised controlled trial highlighted gaps and limitations in the research evidence for FES cycling in people with acquired brain injury. The following points highlight the implications for future research:

- Future larger clinical trials could clarify the effects of FES cycling on strength, although the clinical significance may be limited without accompanying effects on mobility.
- Future clinical trials could limit recruitment to participants who are very weak (i.e. ≤ 2/5 MRC) to clarify the effects of FES cycling on people who cannot easily participate in interventions that require higher levels of strength (i.e. whole task practice of standing up), however there is a large body of evidence indicating that motor training needs to be specific to the task being trained. Therefore, again, any improvements in strength may have limited carry-over to activities other than cycling. Still, there are too few studies of FES cycling in people who are very weak to conclusively rule out a treatment effect in this subgroup of people after acquired brain injury.

Study three: a randomised controlled trial

The aim of this randomised controlled trial was to determine if intensive sit-to-stand training in addition to usual care improves sit-to-stand in people who are unable to stand up independently after stroke.

Study three results

The results of the primary outcome for clinicians' impression of sit-to-stand change and secondary outcomes for sit-to-stand ability, composite strength of the key muscles of the paretic lower limb, sit-to-stand ability, composite strength of the key muscles of the paretic lower limb,

gross lower limb extension strength, the Goal Attainment Scale and ranking of change in ability to move from sitting to standing are presented below:

- The mean between-group difference (95% CI) for clinicians' impression of sit-to-stand change over two weeks was 1.6/15 points (0.0 to 3.1). The upper end of the 95% CI associated with the mean between-group difference for this outcome exceeded the minimally worthwhile treatment effect of 2 points, indicating that the treatment was inconclusive.
- There were no statistically significant between-group differences for sit-to-stand ability, composite strength of the key muscles of the paretic lower limb, or the Goal Attainment Scale. In contrast, there was a statistically significant between-group difference for gross lower limb extension strength of the paretic lower limb (mean between-group difference (95% CI), 6.2 degrees, 0.5 to 11.9). There was also a statistically significant between-group difference for ranking of change in ability to move from sitting to standing (p = value 0.023), supporting the result of the primary outcome measure.

Strengths of study three

The following are strengths of study three:

- Study three was a high quality randomised controlled trial with careful attention given to minimising bias (8/10 points on the PEDro scale).
- The randomised controlled trial protocol was prospectively registered on Australian New Zealand Clinical Trials Registry.
- The manuscript was peer-reviewed and published in the highest-ranked physiotherapy journal.
- There was good adherence to the study protocol and participants in our experimental group performed over three times more sit-to-stand repetitions than participants in our

control group with a median (IQR) of 1252 repetitions (763 to 1773) versus 365 repetitions (164 to 514), respectively.

- The study had broad inclusion criteria. Thus, the results can be generalised to typical patients admitted to sub-acute rehabilitation units after stroke.
- The results clearly demonstrated that an intensive package of sit-to-stand training improves sit-to-stand more than usual care in people who are unable to stand up independently after stroke.
- Our results provide the first evidence from a trial with minimal bias that repetitive sit-to-stand training after stroke maybe worthwhile. Previous trials investigating the effects of repetitive sit-to-stand training have included participants who could already stand up independently or had methodological issues that affected the validity of the results.

Limitations of study three

The following are limitations of study three:

- While we demonstrated that the treatment was statistically significant, the point estimate was imprecise with the upper end of the 95% CI associated with the mean between-group difference exceeding the minimally worthwhile treatment effect of 2 points, suggesting some uncertainty as to whether the treatment effect was clinically worthwhile. A larger sample size would have provided more precision and possibly more clarity around whether the treatment was worthwhile.
- Participants in the study had a wide range of impairments (i.e. aphasia, poor cognition, varied levels of strength) which may have influenced participation with the intervention.
- There was possible contamination between study groups. Physiotherapists may have unintentionally incorporated some of the experimental strategies to improve sit-to-stand into the treatment of control participants. This potential contamination may have

increased the amount of training provided to control participants; thereby decreasing the difference between the two groups.

Implications for future research

This randomised controlled trial highlighted gaps and limitations in the research evidence for intensive sit-to-stand training for people after stroke. The following points highlight the implications for future research:

- Larger clinical trials would provide more precision and possibly more clarity around whether intensive sit-to-stand training is clinically worthwhile.
- There is still uncertainty as to the minimum amount of repetitions of sit-to-stand training required to improve sit-to-stand in people who cannot stand up independently after stroke. Further clinical trials are needed to clarify the effects of different amounts of sit-to-stand training on people's ability to stand up.
- Future clinical trials should limit their recruitment to people who have difficulties standing up independently, thus providing specific data on this subgroup of people after stroke.

Chapter 7 Conclusion

Stroke is one of the leading causes of death and disability. Muscle weakness after stroke can lead to activity limitations and participation restrictions. This thesis contains a discussion of the causes of muscle weakness after stroke, highlighting implications on activity and participation for people who experience weakness. This thesis also contains a literature review of some common interventions used in stroke rehabilitation to improve strength and activity, highlighting the strengths and limitations of current evidence. The studies contained in this research program have answered some important questions. Namely:

1. Do interventions involving repetitive practice improve strength after stroke, and are any improvements in strength accompanied by improvements in activity?
2. Does four weeks of FES cycling in addition to usual care improve mobility and strength in people with a sub-acute acquired brain injury caused by stroke or trauma?
3. Does intensive sit-to-stand training in addition to usual care improve sit-to-stand ability and gross lower limb extension strength in people who are unable to stand up independently after stroke?

These research questions are important to people who experience weakness after stroke because these people often spend weeks, months and years relearning basic tasks such as standing up and walking. Similarly, these research questions are important to therapists and healthcare providers who invest time, effort and resources into stroke rehabilitation programs. These healthcare providers need to know which interventions are the most effective to improve strength and activity after stroke, thus enabling more effective and efficient use of resources to assist people in rehabilitation programs.

The clinical implications of study one are that evidence is now available to therapists and healthcare providers that interventions involving repetitive practice improve strength after

stroke, and that these improvements in strength are accompanied by improvements in activity. Study one also provided estimates for improvement in strength for 12 commonly used interventions after stroke. These estimates inform therapists and healthcare providers which interventions are more likely to improve strength and suggest that repetitive practice should be prioritised as an intervention that can improve both strength and activity in people after stroke. The clinical implications of study two are that FES cycling in addition to usual care may provide more opportunities to improve lower limb strength for people who are very weak and immobile after acquired brain injury caused by stroke or trauma, but there are no accompanied improvements in mobility. Therefore, FES cycling should not be prioritised in stroke rehabilitation programs as an intervention to improve mobility.

The clinical implications of study three are that for people with difficulty standing up after stroke, two weeks of intensive repetitive sit-to-stand training in addition to usual care could be initially prioritised, allowing more time after this period to focus on other tasks requiring independent sit-to-stand ability, such as walking.

Implications for future research

The main implications for future research from this thesis are:

- Further randomised controlled trials with minimal bias are needed. For example, clinical trials need to be prospectively registered on a clinical trial registry and reported according to the CONSORT guidelines.
- All outcome data (i.e. post, change, and participant-level data) should be reported in clinical trials to facilitate more precise analyses and thus better conclusions on clinical effectiveness.
- Future clinical trials of repetitive practice should report dosage as repetitions of active practice rather than scheduled time or time spent in therapy.

- Further clinical trials are needed to clarify the effects of different amounts of repetitive practice on activity limitations and participation restrictions.
- Further large clinical trials are needed to provide more precision around the estimates of treatment effect, thus providing more clarity around whether various strengthening interventions are clinically worthwhile.
- Future clinical trials could limit recruitment to different subgroups of people after stroke (i.e. weak versus very weak). This will clarify the effects of various strengthening interventions on people who cannot easily participate in interventions that require higher levels of strength or activity.
- Further clinical trials are needed to clarify the long-term effects of various strengthening interventions.

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Appendix A Search strategy for study one

Medline
repetitive practice stroke strength.med.v12
medline_24.01.2017_15:20
1. exp Physical Therapy Modalities/ or Occupational Therapy/ or exp Rehabilitation/ or Motor Activity/ or exp Movement/ or exp Psychomotor Performance/ or "Recovery of Function"/ or "Activities of Daily Living"/
2. ((repetiti* or repeat*) adj5 (practi?e or skill or motor or movement or task or performance or train* or retrain* or learn* or relearn*)).tw.
3. (movement* adj4 joint*).tw.
4. (functional adj5 (task* or movement*)).tw.
5. (task* adj3 performance).tw.
6. ((repetiti* or repeat*) adj5 (schedule* or intervention or therap* or program* or regim* or protocol*)).tw.
7. (acquisition adj4 skill*).tw.
8. (muscle* adj5 re-educat*).tw.
9. (exercis* or physiotherapy or physical therapy or occupational therapy or rehabilitation or kinesiotherapy or kinesiology or hydrotherapy or physical performance or locomotion or walking or voluntary movement or psychomotor activity or motor activity or motor performance or (activities adj3 daily living)).tw.
10. (circuit class* or movement technique*).tw.
11. ((function* or motor) adj3 (retraining or re-training or training or relearning or re-learning or learning or recovery)).tw.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. exp stroke/ or brain infarction/ or brain stem infarctions/ or lateral medullary syndrome/ or cerebral infarction/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or stroke, lacunar/
14. exp cerebrovascular accident/ or exp cerebrovascular disease/ or exp cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or basal ganglia hemorrhage/ or brain ischemia/ or brain infarction/ or brain stem infarctions/ or lateral medullary syndrome/ or cerebral infarction/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or hypoxia-ischemia, brain/ or carotid artery diseases/ or carotid artery thrombosis/ or arteriovenous malformations/ or intracranial arteriovenous malformations/ or basal ganglia cerebrovascular disease/ or basal ganglia hemorrhage/ or putaminal hemorrhage/
15. (disease* adj5 carotid arter*).tw.
16. (stroke* or poststroke or post-stroke or apoplex* or cerebral vasc* or cerebralvasc* or cva or SAH).tw.
17. ((brain* or cerebr* or cerebell* or vertebrobasilar artery or intracerebral or intracran* or intra-cranial or basal gangli* or hemisphere* or subarachnoid or arteriovenous or arterio-venous) adj5 (h?emorrhag* or h?ematoma* or bleed* or isch?emi* or infarct* or thrombo* or embol* or occlus* or hypoxi* or lesion* or aneurysm* or insufficiency or malformation* or accident* or arterial disease* or disorder* or disease*)).tw.
18. Hemiplegia/
19. Paresis/

20. (hemiplegia* or hemi-paresis or hemiparesis).tw.
21. acquired brain injur*.tw.
22. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. muscle strength/ or hand strength/ or pinch strength/
24. (motor control or strength* or motricity index or dynamom* or manual muscle test*).tw.
25. ((muscle* adj4 (contraction* or voluntary activation or force* or power)) or maximal voluntary contraction*).tw.
26. muscle contraction/ or isometric contraction/ or isotonic contraction/
27. 23 or 24 or 25 or 26
28. 12 and 22 and 27
29. Randomized Controlled Trials as Topic/
30. randomized controlled trial/
31. Random Allocation/
32. Double Blind Method/
33. Single Blind Method/
34. clinical trial/
35. clinical trial, phase i.pt.
36. clinical trial, phase ii.pt.
37. clinical trial, phase iii.pt.
38. clinical trial, phase iv.pt.
39. controlled clinical trial.pt.
40. randomized controlled trial.pt.
41. multicenter study.pt.
42. clinical trial.pt.
43. exp Clinical Trials as topic/
44. or/29-43
45. (clinical adj trial$).tw.
46. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
47. PLACEBOS/
48. placebo$.tw.
49. randomly allocated.tw.
50. (allocated adj2 random$).tw.
51. or/45-50
52. 44 or 51
53. case report.tw.
54. letter/
55. historical article/
56. 53 or 54 or 55
57. 52 not 56
58. 28 and 57

The Medline search was adapted for searches of all other databases.

PEDro
Search strategy: Advanced
Abstract and Title: 1st search: “stroke” AND “therapy”; 2nd search: “stroke” AND “physi”
Method: Clinical trial

Appendix B Details of interventions of the included studies for study one

Frequency of therapy sessions	2/wk[22] (one study)	3/wk[26,29,31,34,37,39,49,50,55,57,59,61,63,64,67] (15 studies)	4/wk[20,24,28] (three studies)	5/wk[16,17,19,23,25,32,33,35,38,40-48,51,52,54,60,62,65,66] (25 studies)	6/wk[30,56] (two studies)	7/wk[21] participants were advised to administer the intervention independently for this period (one study)	Frequency not stated[58] (one study)	Additional two hours per week over a five-week period[53] (one study)	30 therapy sessions over three weeks[18] (one study)	33 therapy sessions over 12 weeks[36] (one study)	40 therapy sessions over 52 weeks[27] (one study)
Duration of therapy sessions	15-32mins[29,37,40,48,62] (five studies)	30mins[17,21,32,39,43,44,49,54-57,61,63,65] (14 studies)	40-45mins[27,47,60] (three studies)	60mins[18-20,23-26,28,30,33-35,38,41,50,59,67] (17 studies)	60-80mins[52] (one study)	75mins[36] (one study)	90-105mins[22,31,45,46] (four studies)	360mins[16,51] (two studies)	Not stated[42,53,58,64,66] (five studies)		

Intensity of practice (n = 29)	Scheduled therapy time[18,22,35,48,52,60] (six studies)	Target heart-rate reserve or rate of perceived exertion[20,29,34,36,55,67] (six studies)	Graded to individual participants[25,26,30,33,39] (five studies)	Scheduled therapy time but also used 5 RM to set intensity[24,28] (two studies)	Initially increased the speed and amount of repetitions in the higher-intensity groups[45,46] (two studies)	Referred to a threshold of intensity for FES to assist muscle contractions[17,40-44,66] (seven studies)	Increased frequency and amplitude of a vibration platform[63] (one study)				
Progression of practice (n = 35)	Increased amount of repetitions or time performing a task, difficulty or speed, or various combinations of all aspects of progression[18-22,24,26-29,31,33,37-39,45,46,48-50,56,58,59,63] (24 studies)	Adjusted the threshold of intensity for FES to assist muscle contractions[17,40-44,66] (seven studies)	Increased target heart-rate reserve or rate of perceived exertion[34,36,55,67] (four studies)								

Appendix C Activity measures of the upper and lower limb for study one

Upper limb activity measures	Lower limb activity measures
ARAT[21,25,28,30,35,50,53,54] (eight studies)	Self-selected or fast walking speed[20,24,27,32,33,39,49,55,57,62,66,67] (12 studies)
Wolf Motor Function Test[16,18,22,23,36,51] (six studies)	6-minute walk test[29,34] (two studies)
Box and Block Test[31,43,60] (three studies)	Lateral Seated Reach Test - affected side[19] (one study)
Motor Assessment Scale[41,59] (two studies)	Functional Independence Measure - mobility section[40] (one study)
Fugl-Meyer Assessment - upper limb section[45,46] (two studies)	ADL - eight point scale[56] (one study)
Jebsen Taylor Test[47,65] (two studies)	Berg Balance Scale[37] (one study)
Perdue Peg Board Test[26] (one study)	Sensory Organisation Test[63] (standing balance) (one study)
Functional Test for the Hemiparetic Upper Extremity[38] (one study)	Rivermead Mobility Index[52] (one study)
Frenchay Arm Test[58] (one study)	Barthel Index[42] (one study)
Functional Independence Measure - Activities of Daily Living or motor sections[48,61] (two studies)	No measure of activity[17,44,64] (three studies)

Appendix D Relative change from baseline strength for the upper and lower limb, early and late after stroke for study one

	Studies (n)	Participants (n)	SMD	MD (back-converted)	Relative change from baseline
Upper limb combined	25	973	0.16 (95% CI 0.03 to 0.29)	1.28 kg (95% CI 0.24 to 2.32)	15% (95% CI 3 to 26)
Lower limb combined	21	955	0.34 (95% CI 0.22 to 0.47)	5.75 Nm (95% CI 3.72 to 7.94)	28% (95% CI 18 to 39)
Upper limb early	13	668	0.22 (95% CI -0.06 to 0.49)	1.76 kg (95% CI -0.48 to 3.92)	20% (95% CI -5 to 45)
Upper limb late	12	305	0.23 (95% CI 0.00 to 0.46)	2.76 kg (95% CI 0.00 to 5.52)	16% (95% CI 0 to 32)
Lower limb early	8	386	0.48 (95% CI 0.28 to 0.69)	8.11 Nm (95% CI 4.73 to 11.66)	40% (95% CI 23 to 57)
Lower limb late	13	569	0.25 (95% CI 0.08 to 0.42)	2.20 kg (95% CI 0.70 to 3.65)	12% (95% CI 4 to 20)

Appendix E Sensitivity analyses exploring the effects of various methodological aspects of the included studies in the primary meta-analysis for strength for study one

Pooled SMD (Strength)	Adequate randomisation	Concealed allocation	Blinded assessors	Complete outcome data	Reported all outcomes	Free from other threats of bias
n = 46	n=30	n=14	n=31	n=40	n=42	n=8
0.25 (95% CI 0.16 to 0.34)	0.24 (95% CI 0.08 to 0.39)	0.27 (95% CI 0.11 to 0.44)	0.20 (95% CI 0.10 to 0.31)	0.24 (95% CI 0.14 to 0.33)	0.33 (95% CI 0.20 to 0.45)	0.19 (95% CI -0.03 to 0.40)

Appendix F Relative change from baseline strength for the upper limb interventions for study one

Intervention	Studies (n)	Participants (n)	SMD	MD (back-converted)	Relative change from baseline
Assistive technology	2	32	1.02 (95% CI 0.26 to 1.78)	60.18 N (95% CI 15.34 to 105.02)	59% (95% CI 15 to 103)
Bobath	2	294	-0.14 (95% CI -0.37 to 0.09)	NA	NA
CIMT	2	22	1.49 (95% CI 0.44 to 2.54)	4.14 kg (95% CI 1.2 to 7.06)	138% (95% CI 41 to 235)
FES	2	47	0.36 (95% CI -0.23 to 0.96)	NA	NA
Mirror therapy + FES	1	19	0.39 (95% CI -0.52 to 1.30)	NA	NA
Mixed therapies	1	61	0.38 (95% CI -0.13 to 0.89)	NA	NA
Robotics	4	93	0.52 (95% CI 0.10 to 0.94)	0.36/6 points (95% 0.07 to 0.66)	11% (95% CI 2 to 20)
Task-specific training	10	391	0.13 (95% CI -0.07 to 0.33)	NA	NA
Video games	1	14	0.17 (95% CI -0.88 to 1.22)	NA	NA

NA: Not applicable - No back-conversion conducted due to change in baseline strength being non-significant.

Appendix G Relative change from baseline strength for the lower limb interventions for study one

Intervention	Studies (n)	Participants (n)	SMD	MD (back-converted)	Relative change from baseline
Bobath	1	65	0.23 (95% CI -0.26 to 0.72)	NA	NA
Cycling	2	104	0.49 (95% CI 0.10 to 0.88)	137.54 N (95% CI 28.07 to 247.02)	20% (95% CI 4 to 36)
FES	3	107	0.45 (95% CI 0.07 to 0.84)	11.79 Nm (95% CI 1.83 to 22.01)	39% (95% CI 6 to 74)
Mirror therapy + FES	1	27	0.79 (95% CI -0.00 to 1.57)	NA	NA
Mixed therapies	1	18	0.25 (95% CI -0.69 to 1.18)	NA	NA
Robotics	1	9	1.36 (95% CI -0.20 to 2.91)	NA	NA
Task-specific training	8	540	0.27 (95% CI 0.09 to 0.44)	2.35 kg (95% CI 0.78 to 3.83)	13% (95% CI 4 to 21)
Video games	1	40	0.00 (95% CI -0.62 to 0.62)	NA	NA
Water-based exercise	1	12	1.17 (95% CI -0.11 to 2.45)	NA	NA
Whole-body vibration	2	33	0.84 (95% CI 0.10 to 1.58)	18.82 Nm (95% CI 2.24 to 35.39)	21% (95% CI 3 to 39)

NA: Not applicable - No back-conversion conducted due to change in baseline strength being non-significant.

Appendix H The effect of repetitive practice versus no intervention or sham on *upper limb strength* for study one

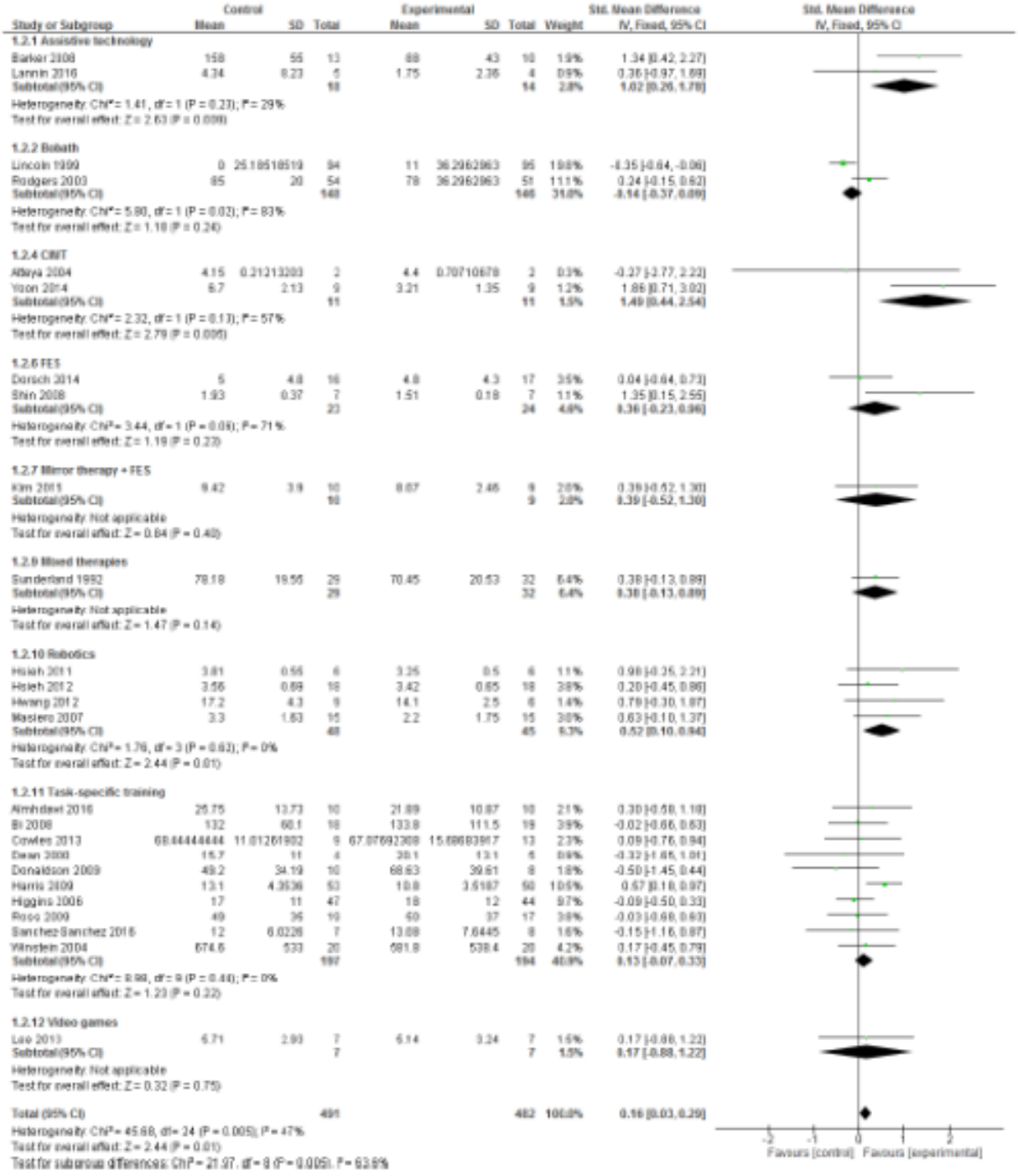

Figure 6. The effect of repetitive practice versus no intervention or sham on *upper limb strength* (n = 973). Effects are expressed as SMD (95% CI).

Appendix I The effect of repetitive practice versus no intervention or sham on *lower limb strength* for study one

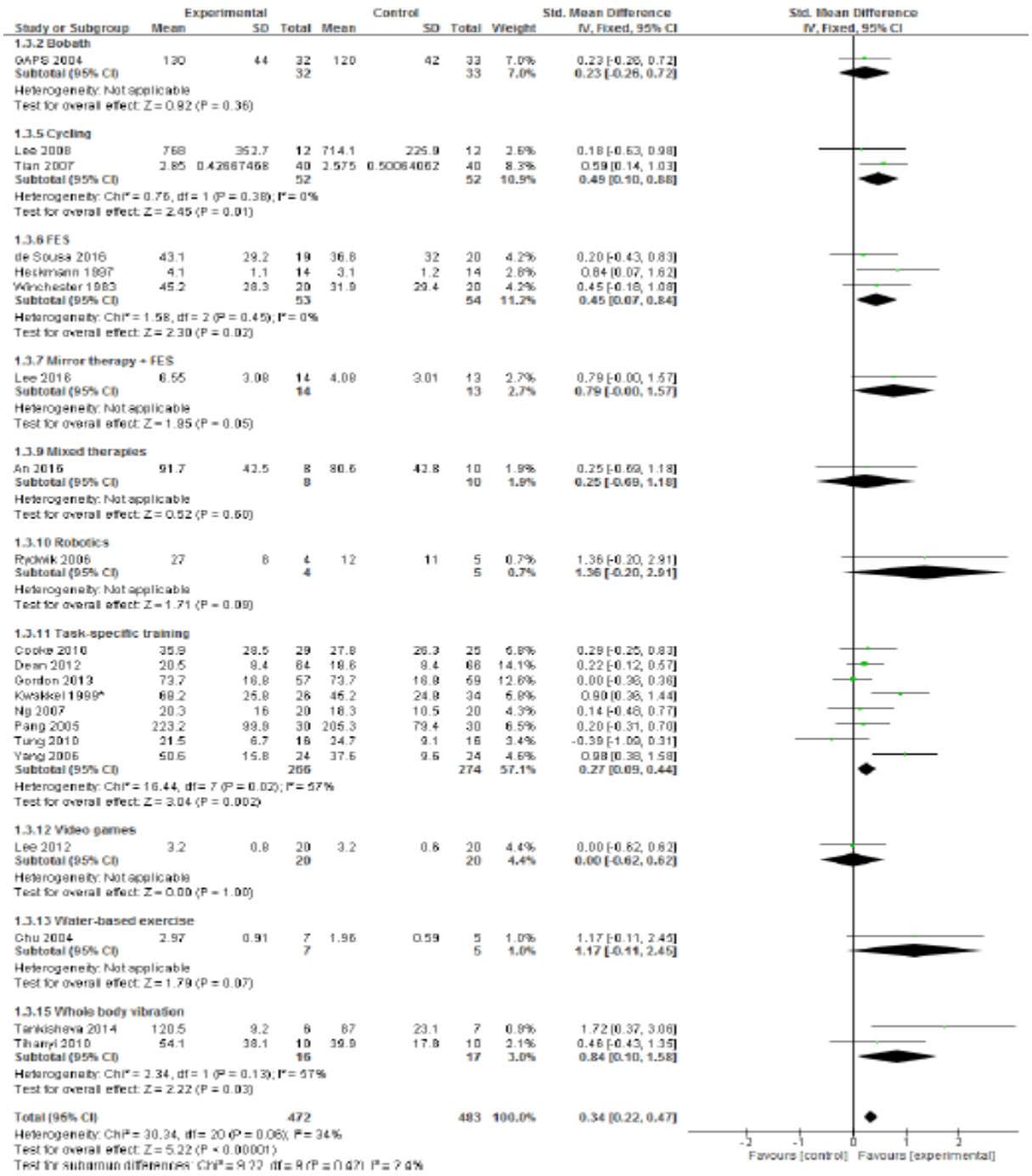

Figure 7. The effect of repetitive practice versus no intervention or sham on *lower limb strength* (n = 955). Effects are expressed as SMD (95% CI). *Means (SD) obtained from Cooke et al 2010.

Appendix J Individual participant data for study two

		Mobility		Strength of the knee extensors of the affected lower limb		Strength of key muscles of the affected lower limb		Strength of the knee extensors of the unaffected lower limb		Spasticity of the ankle plantar flexors of the affected lower limb	
		(0 to 21)		*(Nm)*		*(0 to 20)*		*(Nm)*		*(0 to 5)*	
ID	Group	Week 0	Week 4	Week 0	Week 4	Week 0	Week 4	Week 0	Week 4	Week 0	Week 4
1	Con	3	12	30.64	34.81	6	6	96.78	79.72	2	0
2	Con	9	20	16.78	28.44	10	14	26.45	39.25	3	3
3	Con	12	19	86.36	130.37	8	8	125.37	133.04	2	0
4	Con	3	3	11.18	23.83	8	9	42.07	48.25	0	1
5	Con	3	6	17.92	12.23	3	3	30.15	49.20	0	1
6	Con	3	3	0.00	0.00	0	0	37.01	51.35	0	1
7	Con	13	18	32.68	42.01	14	13	40.91	56.02	0	0
8	Con	14	19	63.55	66.49	17	15	48.84	63.55	2	3
9	Con	3	3	9.53	19.59	6	8	59.84	66.46	0	0
10	Con	3	3	0.00	9.61	0	1	22.65	32.95	0	2
11	Con	3	3	8.34	12.99	7	9	26.97	42.90	2	1
12	Con	5	17	64.02	71.55	13	13	87.55	87.87	0	2
13	Con	6	11	38.83	57.90	12	11	82.37	84.18	0	2
14	Con	17	20	71.14	43.60	15	16	84.52	65.02	1	0
15	Con	3	7	22.75	38.68	2	6	51.19	60.58	0	2
16	Con	8	20	47.07	28.24	14	12	60.31	51.78	0	1
17	Con	6	19	51.78	76.20	8	13	94.44	83.26	2	2
18	Con	4	18	20.59	39.47	5	8	57.66	81.35	0	0
19	Con	3	4	0.00	0.00	0	0	71.86	81.91	0	2
20	Con	3	3	5.15	0.00	3	5	27.21	36.04	3	2
1	Exp	5	8	0.00	50.48	0	3	71.20	84.46	3	2
2	Exp	12	18	0.00	69.20	4	8	70.96	98.50	3	3
3	Exp	3	7	9.10	22.59	5	11	52.72	72.18	0	1
4	Exp	12	18	64.53	68.37	12	14	76.61	76.88	3	4
5	Exp	3	5	38.25	28.83	10	7	40.31	34.72	0	0
6	Exp	3	9	33.54	34.13	6	6	70.90	65.90	3	4
7	Exp	3	4	0.00	0.00	0	2	30.60	37.95	0	2
8	Exp	5	12	61.11	56.18	11	18	105.46	86.40	3	3
9	Exp	9	20	90.69	117.37	5	15	114.86	153.45	3	3
10	Exp	3	3	0.00	17.59	0	4	51.25	49.97	0	0
11	Exp	3	9	21.62	66.24	7	13	24.37	86.84	2	1
12	Exp	3	5	0.00	31.00	1	6	51.48	57.73	3	4
13	Exp	6	20	15.93	24.44	11	19	24.99	23.34	0	2
14	Exp	3	6	22.36	42.07	4	13	95.91	82.67	2	3
15	Exp	5	5	24.48	20.08	9	15	40.17	35.77	3	3
16	Exp	16	21	62.61	84.22	14	16	100.62	104.34	0	0
17	Exp	5	18	31.28	48.35	7	12	52.04	52.33	2	2
18	Exp	3	3	4.41	2.06	3	3	80.61	82.38	3	2
19	Exp	3	.	26.36	.	7	.	36.01	.	0	.
20	Exp	5	7	61.12	35.03	13	15	86.83	61.12	2	0

Appendix K Individual participant data for study three

		Clinicians' impression of sit-to-stand change		Sit-to-stand ability		Composite strength of key muscles of the affected lower limb		Gross lower limb extension strength		Goal Attainment Scale		Ranking of change in participants'ability to move from sitting to standing	
		(/15 points)		*(/6 points)*		*(/15 points)*		*(deg)*		*(/5 points)*		*(rank)*	
ID	Group	Week 0	Week 2	Week 0	Week 2	Week 0	Week 2	Week 0	Week 2	Week 0	Week 2	Week 0	Week 2
2	Exp	NA	3.5	2	4	9	9	25	22.5	NA	0	NA	-4.5
5	Exp	NA	6	1	2	2	3	5	30	NA	-1	NA	-4.5
6	Exp	NA	4	2	2	7	5	27.5	30	NA	1	NA	-7
9	Exp	NA	1	1	1	5	0	5	12.5	NA	-2	NA	-2.5
10	Exp	NA	7	2	5	6	9	17.5	25	NA	2	NA	0
12	Exp	NA	4	2	3	7	10	17.5	22.5	NA	1	NA	-3
13	Exp	NA	6	2	6	11	13	25	45	NA	-1	NA	2.5
20	Exp	NA	4	5	5	4	6	17	27.5	NA	2	NA	1
23	Exp	NA	6	2	5	6	10	17.5	25	NA	1	NA	-2
24	Exp	NA	4.5	3	6	10	12	27.5	40	NA	2	NA	-2.5
25	Exp	NA	5	2	5	9	11	32.5	30	NA	2	NA	3
26	Exp	NA	5.5	2	3	10	10	17.5	30	NA	-1	NA	6
27	Exp	NA	7	4	6	13	14	65	77.5	NA	2	NA	0
28	Exp	NA	3.5	1	2	4	6	17.5	22.5	NA	0	NA	1.5
30	Exp	NA	6	2	3	0	2	2.5	17.5	NA	2	NA	3
1	Con	NA	-1	5	6	10	10	27.5	30	NA	0	NA	1
3	Con	NA	5	2	2	5	6	7.5	17.5	NA	0	NA	-1
4	Con	NA	6.5	3	5	6	5	20	20	NA	1	NA	-0.5
7	Con	NA	-1.5	1	1	5	6	12.5	10	NA	-2	NA	-0.5
8	Con	NA	3	5	6	6	9	40	42.5	NA	2	NA	-0.5
11	Con	NA	4	4	6	0	3	17.5	0	NA	-1	NA	3.5
14	Con	NA	6.5	4	6	9	9	15	25	NA	2	NA	-0.5
15	Con	NA	1	2	3	6	6	12.5	12.5	NA	-1	NA	0.5
16	Con	NA	2.5	1	2	5	5	17.5	27.5	NA	-1	NA	-1.5
17	Con	NA	3.5	3	5	11	14	25	25	NA	0	NA	5
18	Con	NA	2	4	6	10	12	37.5	37.5	NA	-1	NA	1
19	Con	NA	4	5	6	9	12	35	40	NA	0	NA	-3.5
21	Con	NA	6	1	2	5	6	10	20	NA	0	NA	-1.5
22	Con	NA	5	3	3	10	8	32.5	45	NA	0	NA	4.5
29	Con	NA	3	5	6	9	11	15	17.5	NA	0	NA	3